The Impact of Adult Attention Deficit/ Hyperactivity Disorder, Methylphenidate, and the *COMT* Val^{158}Met Polymorphism on Selective Attention and Working Memory

Der Einfluss von Aufmerksamkeitsdefizit-/ Hyperaktivitätsstörung bei Erwachsenen, Methylphenidat, und des *COMT* Val^{158}Met Polymorphismus auf selektive Aufmerksamkeit und Arbeitsgedächtnis

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Table of Abbreviations

aADHD	Adult attention deficit/ hyperactivity disorder
ANOVA	Analysis of variance
ASRS	Adult ADHD Self-Report Scale
BOLD	Blood oxygenation level-dependent
CAARS	Conners' Adult ADHD Rating Scales (long version)
COMT	Catechol-*O*-Methyltransferase
dACC/ ACC	(Dorsal) anterior cingulate cortex
DAT	Dopamine transporter
DLPFC/ PFC	(Dorsolateral) prefrontal cortex
DSM	Diagnostic and Statistical Manual of Mental Disorders
EEG	Electroencephalography
EF	Executive functions
EPI	Echo planar imaging
ERP	Event-related potential
FFA	Fusiform face area
fMRI	Functional magnetic resonance imaging
FWE	Family-wise error
GWAS	Genome-wide association studies
IFG/MFG/SFG	Inferior/ middle/ superior frontal gyrus
IPS	Intraparietal sulcus
IR	Immediate release
Met	Methionine
MNI	Montréal Neurological Institute
MPH	Methylphenidate
MRB	Research Center for Magnetic-Resonance-Bavaria
NET	Norepinephrine transporter
OROS	Osmotic-release oral system
PANAS	Positive and Negative Affect Schedule
PCC	Posterior cingulate cortex
PET	Positron emission tomography
PPA	Parahippocampal place area
REX	Region of Interest Extraction
ROI	Region of interest
SNP	Single-nucleotide polymorphism
SPM	Statistical Parametric Mapping
StPM	Standard Progressive Matrices
TR	Repetition time
Val	Valine
WAIS	Wechsler Adult Intelligence Scale
WCST	Wisconsin Card Sorting Test
WURS	Wender Utah Rating Scale

Zusammenfassung

Theorien zur Ätiologie der Aufmerksamkeitsdefizit-/ Hyperaktivitätsstörung (ADHS) konzentrieren sich oft auf defizitäre Prozesse der Verhaltensinhibition, die wiederum zu Defiziten der Exekutivfunktionen (EF) führen. Übereinstimmend mit diesen Beeinträchtigungen berichteten Neuroimaging-Studien von Hypoaktivierung im frontoparietalen Netzwerk sowie Hyperaktivierung im dorsalen Aufmerksamkeitsnetzwerk. Studien zur Wirkung von Stimulanzien zeigten eine Verbesserung von EF-Maßen einschließlich des Arbeitsgedächtnisses sowie eine Hochregulierung des aufgabenpositiven/ frontoparietalen Netzwerks durch Methylphenidat (MPH). Bis jetzt untersuchten nur wenige Studien die Auswirkungen von ADHS auf neurophysiologische und Verhaltensmaße der EF sowie den Effekt von länger andauernder Stimulanziengabe bei erwachsenen Patienten.

Die Wichtigkeit des Enzyms Catechol-*O*-Methyltransferase (COMT) für subkortikale und kortikale dopaminerge und noradrenerge Funktionen führte darüber hinaus zu Studien, die eine potentielle Interaktion in der Wirkung des *COMT* Genotyps und ADHS auf neuropsychologische Funktionen und insbesondere auf das Arbeitsgedächtnis untersuchten. Die Ergebnisse dieser Studien waren recht heterogen. Da zudem keine der Studien die Ergebnisse der ADHS-Patienten mit denen einer gesunden Kontrollgruppe verglich, konnten möglicherweise vorhandene unterschiedliche Einflüsse von *COMT* bei Patienten und gesunden Kontrollprobanden nicht angemessen ermittelt werden.

Das Ziel dieser Dissertation waren zunächst die Untersuchung von selektiven Aufmerksamkeitsprozessen, die durch die Zentrale Exekutive vermittelt werden, sowie die Übertragung der dazu verwendeten Arbeitsgedächtnisaufgabe ins fMRT. Eine dritte Studie strebte die Untersuchung der Auswirkungen von ADHS bei Erwachsenen (aADHS), MPH und *COMT* Genotyp auf das Arbeitsgedächtnis an. Ein besonderer Fokus bei der Analyse der fMRT-Daten lag hierbei auf der Aktivierung des aufgabenpositiven Netzwerks.

Die erste Studie (EEG) konnte bisherige Forschungsergebnisse replizieren und erweitern. Zudem konnte diese Studie die Gesamtaktivierung in frontalen Bereichen mit der Unterdrückungseffizienz in posterioren visuellen Bereichen in Verbindung bringen sowie einen Einfluss von hyperaktiv/ impulsiver ADHS-Symptomatik auf die Verhaltensleistung feststellen. Die zweite Studie (fMRT) zeigte eine erfolgreiche Übertragung des Paradigmas auf das fMRT und eine weitergehende Replizierung und Erweiterung vorheriger Forschungsergebnisse. Es konnte außerdem die Sensitivität der Aufgabe für die Effekte des *COMT* Genotyps gezeigt werden. Die dritte Studie (fMRT) war eine der ersten Studien, die exploratorisch die Effekte von *COMT* in einer Stichprobe von aADHS-Patienten und einer vergleichbaren gesunden Kontrollgruppe untersuchte. Hier zeigte sich eine Interaktion von *COMT* Genotyp und aADHS auf die erhobenen neuropsychologischen Maße sowie auf die fMRT-Aktivierung während einer n-back Arbeitsgedächtnisaufgabe. Die Aufgabe führte zu mehr Aktivierung im aufgabenpositiven Netzwerk der aADHS-Gruppe im Vergleich zur Kontrollgruppe. Da keine Leistungsunterschiede zwischen den Gruppen zu erkennen waren, weist diese Hyperaktivierung auf eine kompensatorische Aktivierung in der aADHS-Gruppe hin. Zudem zeigte sich eine erhöhte Aktivierung im Frontalkortex bei Patienten, die MPH statt einem Placebo einnahmen. Die fMRT-Daten der Aufgabe zur selektiven Aufmerksamkeit zeigten außerdem eine reduzierte Aktivierung im rechten DLPFC der Patientengruppe, die über alle Probanden hinweg mit einer reduzierten Unterdrückungseffizienz assoziiert war. Der klinische Effekt von MPH in der Patientenstichprobe war sichtbar, erreichte aber keine Signifikanz, was vermutlich auf eine zu geringe experimentelle Power zurückzuführen ist.

Die Studien in dieser Dissertation konnten vorherige Befunde erfolgreich replizieren und erweitern. Ein Ziel für zukünftige Studien sollte die weitergehende Untersuchung dieser Fragestellungen sein. Vor allem in Bezug auf eine Interaktion von *COMT* Genotyp und aADHS auf neuropsychologische Testergebnisse und fMRT-Aktivierung, aber auch auf Medikamenten-Response und Nebenwirkungen ist dies von großer Bedeutung. Die Übernahme einer Netzwerkperspektive bei der Analyse von fMRT-Daten scheint zudem der beste Weg, existierende Unterschiede zwischen den Gruppen zu finden.

Abstract

Theories of attention deficit hyperactivity disorder (ADHD) aetiology have placed a focus on impaired behavioural inhibition presumably leading to executive function (EF) deficits. Neuroimaging studies report neurophysiological findings consistent with these hypothesised impairments, and investigations of functional brain activation from a network perspective report hypoactivation in the frontoparietal network as well as hyperactivation in the dorsal attention network. Studies investigating the acute effects of stimulant medication on EF show an improvement on behavioural EF measures including working memory. In addition, methylphenidate (MPH) was shown to up-regulate the task-positive/ frontoparietal network in children and adolescents with ADHD. So far, there are only few studies investigating the impact of ADHD on behavioural and neurophysiological EF measures as well as the effect of several weeks of stimulant medication in adult patients.

The importance of the catechol-*O*-methyltransferase (COMT) enzyme for subcortical and cortical dopaminergic and noradrenergic functioning furthermore led to studies investigating a potential interactive impact of *COMT* genotype and ADHD on neuropsychological functioning, with a particular focus on working memory. The results of these studies were very heterogeneous. In addition, as none of the studies compared the results of ADHD patients to those of a healthy control group, possible differential effects of *COMT* in patients and healthy controls could not be examined.

The aim of this dissertation was to investigate selective attention properties of the central executive component during a working memory task and to transfer this task to fMRI. A third study then aimed to investigate the effects of adult ADHD (aADHD), MPH, and COMT genotype on working memory with a particular focus on activation of the task-positive network during the analysis of the fMRI data.

The first study (EEG) could replicate and extend the results from previous research. This study could furthermore connect the overall activation in frontal

areas to suppression efficiency in posterior visual areas as well as establish the impact of hyperactive/ impulsive ADHD symptoms on task performance. The second study (fMRI) allowed the successful transfer of the paradigm to fMRI, and the further replication and extension of previous findings. In addition, this study showed the sensitivity of the task to the effects of the *COMT* genotype. The third study (fMRI) was one of the first studies that exploratorily investigated the effects *COMT* in a sample of aADHD patients and a comparable healthy control group. This study showed an interactive effect of these two factors on neuropsychological measures as well as on fMRI activation during a classic n-back working memory task. In addition, this task led to more activation in the task-positive network of the aADHD group compared to a healthy control group in the absence of performance differences, pointing towards compensatory activation in the aADHD group. Furthermore, activation in the frontal cortex was increased in patients taking MPH compared to a placebo. The fMRI data from the selective attention task moreover showed decreased activation in the right DLPFC of the patient group, which was associated with reduced suppression efficiency across all participants. The clinical effect of MPH in the third study was visible but did not reach significance, which is probably attributable to a lack of experimental power.

The studies in this dissertation could successfully replicate and extend previous findings. A goal for future studies should be the further investigation of the interactive effects of *COMT* genotype and aADHD on neuropsychological test results and fMRI activation, but also on medication response and adverse effects. In this context, the adaptation of a network perspective during the analysis of fMRI data seems to be the best way to detect existing between-group differences.

1 Introduction

> People with ADHD are difficult to deal with. They are hard on everybody else, and they are especially hard on themselves, even if they do seem to be nothing more than hedonistic fun-seekers. Too many internalize the feeling held by others that they are incorrigibly flawed, deficient, disposable people with little to offer to society. Too many are abandoned to inadequate educational systems and parental support networks and grow up to become unsocialized, unqualified, problematic and emotionally erratic adults. Too many spend their lives hurting themselves and others, endlessly apologizing for their actions in the hope that the apology will dismiss the behavior that caused the pain as if it were a bad dream that never happened. But it did. And it will not go away. Ever.
>
> Richard Kuendig in *ADHD: An Autobiography of Survival* (2003, p.15).

These words by Richard Kuendig, a clinical psychologist who himself suffers from adult attention deficit/ hyperactivity disorder (aADHD) dramatically describe the long-term consequences of a disorder that was once thought to subside in adolescence. The conception of ADHD as a childhood disorder that you just 'outgrow' is still widespread and research has only relatively recently recognized that this might not be the case for most of the affected children. ADHD is in fact a disorder that subtly and pervasively affects neurophysiological functioning leading to altered attentional and emotional processes. While research on childhood ADHD abounds, much work remains to be done on how this disorder affects adults, and few studies exist on the influence of pharmacological treatment on adult brain function. This dissertation therefore aims to contribute to the understanding of attentional processes in aADHD, the pharmacological treatment of its symptoms, and the possible interaction of aADHD and a common variation of the *COMT* gene, which might ameliorate or exacerbate existing symptoms.

1.1 Adult ADHD and Its Treatment

1.1.1 Diagnosis, Prevalence, and Persistence

The first well-known description of ADHD in children dates back as far as 1845 (Lange, Reichl, Lange, Tucha, & Tucha, 2010): Heinrich Hoffman described two children, with one – Fidgety Phil – exhibiting severe symptoms of hyperactivity with an inability to sit still, and the other – Johnny Head-in-Air – showing pronounced symptoms of inattention. The disorder now known as ADHD was subsequently described as a "defect in moral control", "postencephalitic behavior disorder", "hyperkinetic disease of infancy", "minimal brain damage", and "minimal brain dysfunction" before the second edition of the Diagnostic and Statistical Manual of Mental Disorders (DSM-II) (American Psychiatric Association, 1968) introduced the condition as "Hyperkinetic Reaction of Childhood". In 1980, the DSM-III (American Psychiatric Association) changed the focus from hyperkinesis to attentional dysfunction by specifying the diagnostic criteria for attention deficit disorder (ADD), with and without hyperactivity. However, the revision of this edition (DSM-III-R) (American Psychiatric Association, 1987) provided an equal focus on symptoms of both inattention and hyperactivity/ impulsivity by naming the condition attention deficit/ hyperactivity disorder (ADHD) for the first time, before the DSM-IV-TR (American Psychiatric Association, 2000) described the current symptoms and provided further diagnostic specificity by distinguishing between three different subtypes based on the individual distribution of symptoms (see Table 1.1).

The recently published latest revision, DSM-5 (American Psychiatric Association, 2013), only makes slight changes to these criteria. However, special efforts were undertaken to better include adult presentations of ADHD in the definition of the disorder. While the diagnostic criteria remain the same, examples now specify how symptoms may present in adolescence and adulthood, e.g. instead of inappropriately leaving their seats, older adolescents and adults may be more likely to endure a distressing subjective feeling of restlessness in situations where they are expected to remain seated for a lengthy amount of time. Emotional lability

as an impairment that is rather common in aADHD and independent of underlying comorbid conditions (Skirrow & Asherson, 2013) was, however, not included in the new symptoms list. The DSM-5 (2013) also slightly lowers the diagnostic threshold for adults over the age of 17 years and now only requires five symptoms from one (or both) of the categories for a diagnosis.

Table 1.1: Overview of the diagnostic criteria for ADHD according to the DSM-IV-TR (2000).

Symptoms	
Inattention	*Hyperactivity/ Impulsivity*
Careless mistakes	Fidgeting or squirming
Difficulty sustaining attention	Leaving one's seat
Not listening	Inappropriate running or climbing
Failure to finish tasks	Difficulty playing quietly
Difficulty organizing tasks	Often 'on the go'
Dislike of sustained mental effort	Excessive talking
Loss of necessary things	Blurting out
Easily distracted	Difficulty awaiting turn
Forgetful	Interrupting or intruding
Six or more symptoms: → Predominantly inattentive type	Six or more symptoms: → Predominantly hyperactive-impulsive type
Criteria for both subtypes are met: → Combined type	
Necessary preconditions: • Symptoms persist for at least six months. • Some symptoms are present before the age of seven years. • Symptoms cause some impairment in two or more settings. • Clear evidence of significant impairment in social, academic, or occupational functioning.	

While there are numerous studies investigating the prevalence of ADHD in children and adolescents, studies of ADHD prevalence in adults are still

comparably rare. A German study reports a prevalence rate of 4.7 % in a large population sample aged 18 to 64 years (de Zwaan et al., 2012). Younger participants met criteria for ADHD more often than older participants and ADHD symptoms were associated with lower education, unemployment, depression, and anxiety, but not with gender. An Australian study of a large middle-aged sample with a mean age of 50 years reports a slightly higher ADHD prevalence of 6.2 % (Das, Cherbuin, Butterworth, Anstey, & Easteal, 2012). As in the German study, there was no gender difference, and participants with more ADHD symptoms suffered from higher depression and anxiety and scored lower on measures of employment, financial and general well-being, relationship quality, and health. A Dutch study investigated a sample of older adults aged 60 to 94 years (Michielsen et al., 2012). These researchers found that 2.8 % of participants met full diagnostic criteria of ADHD with an additional 4.2 % showing four or more symptoms of any one of the three subtypes. As in the previous studies, ADHD symptoms declined with increasing age. A recent meta-analysis puts the prevalence of ADHD according to DSM-IV (2000) at 5.9 % to 7.1 % for children and adolescents, and at 5.0 % for young adults (Willcutt, 2012). Importantly, these researchers found no significant differences in the prevalence rates for different regions or countries. This finding supports ADHD as a valid diagnostic construct.

Studies furthermore indicate a substantial stability of ADHD symptoms over time: A ten-year follow-up study of children aged 6 to 17 years at the first assessment points to a substantial persistence of ADHD symptoms (Biederman, Petty, Evans, Small, & Faraone, 2010). While 35 % of participants still met full diagnostic criteria at follow-up, another 43 % still showed subthreshold symptoms or functional impairment. These participants also presented with increased psychiatric comorbidity and stronger educational and interpersonal impairment. Furthermore, a Swedish study showed that 53.3 % of older adults (aged 65 to 80 years) who were retrospectively diagnosed with childhood ADHD still scored above the cut-off on a present-day rating scale (Guldberg-Kjar, Sehlin, & Johansson, 2013). A meta-analysis of follow-up studies of children with ADHD reports persistence rates of around 15 % at age 25 years when full diagnostic criteria had

to be fulfilled, but of around 65 % when also partially remitted cases were included (Faraone, Biederman, & Mick, 2006).

In addition, longitudinal studies of participants diagnosed with ADHD in childhood or adolescence support the association of ADHD and worsened life outcomes: A study following a community sample of adolescents over twenty years found an association of ADHD symptoms in adolescence and impaired physical and mental health, lower work performance, and increased financial stress in later life (Brook, Brook, Zhang, Seltzer, & Finch, 2013). A 16-year longitudinal study reports higher lifetime rates of psychiatric disorders and increased impairment in psychosocial and educational functioning in adults originally diagnosed with childhood ADHD compared to a case-control group (Biederman et al., 2012). In addition, a study of an adult patient sample found significantly lower educational attainment and a lower level of employment than in the general population (Gjervan, Torgersen, Nordahl, & Rasmussen, 2012). Interestingly, a later begin of stimulant treatment was associated with worse employment outcomes.

1.1.2 Pharmacological Treatment

The first treatment attempt of children with ADHD using stimulant medication was implemented by Charles Bradley in the 1930s (Conners, 2000; Lange et al., 2010). He had administered the strong stimulant Benzedrine to hospitalized children for medical reasons and noted a paradoxical effect of improved school performance and decreased motor activity in some of the treated children. According to the findings of a subsequent more systematic clinical trial, the most improved children were those who exhibited what would today be considered typical symptoms of ADHD: attentional problems, hyperactivity/ impulsivity, and emotional instability. In 1944, Leandro Panizzon synthesized the stimulant drug methylphenidate (MPH), which he named Ritalin in honour of his wife (Lange et al., 2010). MPH turned out to be very effective in treating the symptoms of ADHD and – unlike Benzedrine – is still widely used today.

The stimulant properties of MPH are attributed to its capability to block the functioning of the dopamine transporter (DAT) (Schweri et al., 1985; Volkow et al., 2001; Volkow et al., 1998) and the norepinephrine transporter (NET) as well as – to a lesser extent – to inhibit monoamine oxidase, an enzyme deactivating catecholamine neurotransmitters like dopamine and norepinephrine (Pliszka, 2005). DAT are located at the terminal button of axons and act by transporting excess dopamine from the synaptic cleft back into the neuron, thereby decreasing extracellular dopamine concentrations. Their main expression site is the striatum with only scarce expression in other areas (Lewis et al., 2001; Sesack, Hawrylak, Matus, Guido, & Levey, 1998). A landmark positron emission tomography (PET) study by Volkow and colleagues (Volkow et al., 1998) could show that MPH was extremely effective at blocking the DAT, occupying more than fifty per cent of transporters in the striatum at therapeutic doses. These findings were confirmed in adult patients with ADHD who showed increased DAT availability in the striatum, with methylphenidate acting by lowering this availability and thereby increasing synaptic dopamine concentrations (Krause, Dresel, Krause, Kung, & Tatsch, 2000; Krause, Dresel, Krause, la Fougere, & Ackenheil, 2003; Volkow et al., 2007).

In contrast to DAT, NET is also expressed in the cortex and can take up norepinephrine as well as dopamine, thereby playing an important role in the regulation of dopamine levels in the prefrontal cortex (PFC) (Pliszka, 2005). Unfortunately, the PET and single-photon emission computed tomography (SPECT) imaging used to investigate the subcortical action of stimulant medication is not sensitive enough to detect changes in cortical catecholamine neurotransmission (Arnsten, 2006). The precise impact of stimulant medication in this region is therefore still somewhat unclear. However, an *in vivo* study in rats demonstrated that therapeutic doses of MPH caused a significant increase in norepinephrine and dopamine release in the PFC while improving attention and working memory (Berridge et al., 2006).

The efficiency of stimulants to increase both dopamine and norepinephrine concentrations in the synaptic cleft can also be related to Grace's (1991) tonic-phasic model of dopaminergic function (see also 1.2.1) (Pliszka, 2005). According

to the tonic-phasic model of dopaminergic function, increased tonic (background) neurotransmitter release of dopamine (and norepinephrine) leads to increased synaptic concentrations of this neurotransmitter, which in turn activates the neurons' auto-receptors. These auto-receptors then down-regulate the responsivity of the neurotransmitter system to external events by inducing a decrease of phasic (event-related) activity (Grace, 1991). In the case of ADHD, medication might operate to increase tonic neurotransmitter release and thereby reduce the activity of an overly active and therefore unstable and disorganised phasic dopaminergic (and noradrenergic) system (Arnsten, 2006; Pliszka, 2005). As the dopaminergic and noradrenergic neurotransmitter systems are closely linked, the individual impact of these two systems on cognition can currently not be separated. It is, however, notable that medications which primarily influence the dopaminergic system so far showed no effectiveness in the treatment of ADHD (Pliszka, 2005).

Studies investigating MPH treatment in aADHD patients vary considerably in terms of design, medication schedule, MPH formulation, and employed symptom ratings: A recent long-term double-blind placebo-controlled study tested efficacy, tolerability, and safety of long-acting osmotic-release oral system (OROS) MPH in 223 adults diagnosed with ADHD (Biederman, Mick, et al., 2010). In order to be included in the study, participants had to fulfil diagnostic criteria for ADHD according to DSM-IV-TR (2000) and be without an adequate trial of MPH in the past. The authors randomly assigned participants to either MPH or placebo treatment and used a free dose titration schedule. In this schedule, medication dose could be flexibly adjusted based on patients' reports of subjective improvement and adverse effects. The maximum allowed dose was 1.3 mg/kg per day and a mean daily dose of 78.4 ± 31.7 mg was achieved after six weeks of treatment. ADHD symptoms were assessed using the Adult ADHD Investigator Symptom Rating Scale (AISRS), a semi-structured interview (Spencer et al., 2010). After six weeks of either MPH or placebo treatment, patients in the MPH group showed significantly more improvement with significantly more responders in this group than in the placebo group (67 % versus 37 %). A following 24-week trial with the responders from both groups showed no difference between the MPH and

the placebo group with regard to stability of the response. MPH responders were subsequently randomised to a 4-week discontinuation trial, where they were assigned either their previous MPH medication or were switched to a placebo. Interestingly, although the placebo group showed a slight worsening of their symptoms and the MPH group showed some further improvement, there was no significant difference with regard to relapse rate between the two groups.

A double-blind forced titration trial over six weeks yielded similar results: Spencer and colleagues (2005) investigated MPH treatment in 146 aADHD patients and report significantly higher response rates of the MPH group compared to the placebo group based on investigator ratings, but also slightly more adverse effects the form of appetite suppression, dry mouth, moodiness, and weight loss. The immediate-release (IR) MPH medication used in this study was prescribed up to a maximum dose of 1.3 mg/kg per day with a mean dose of 82 ± 22 mg achieved after six weeks. The MPH medication used in this study was supplied by Novartis Pharmaceuticals Corporation and was most likely Ritalin®. The company does not give any explicit recommendations for maximum daily dosage in adults, but states that the average dosage is 20 mg to 30 mg per day (Novartis Pharmaceuticals Corporation), which makes the average daily dosage used in this study appear rather high.

Medori and colleagues (2008) report the results of a double-blind fixed dose trial with 401 aADHD patients. Patients received either a daily dose of 18 mg, 36 mg, or 72 mg MPH or a placebo, with 72 mg/day being the maximum recommended adult dose of Concerta®, the extended-release MPH medication used in this study (Janssen Pharmaceuticals). This trial also yielded significantly more improvement in the three MPH groups compared to the placebo group with effect sizes of .38, .43, and .72, respectively. There were also significantly more responders in the MPH groups (between 48.5 % and 59.6 %) compared to the placebo group (27.4 %) when observer ratings on the Conners' Adult ADHD Rating Scales (CAARS) (Conners, Erhardt, & Sparrow, 1999) were examined. When CAARS self-report ratings were considered, the placebo group also showed significantly less improvement than the 72 mg/day MPH group across the scales incorporating adult symptoms as well as on the total and index score scales, but differences were

less stable when the placebo group was compared to the 18 mg/day and 36 mg/day MPH groups. In addition, all MPH groups showed more adverse effects in the form of decreased appetite, headache, and insomnia with some of these effects being dose-dependent.

A large German multi-centre study of extended-release MPH medication investigated 359 aADHD patients for 24 weeks in a double-blind placebo-controlled design (Rösler et al., 2009). Although the maximum daily dose of 60 mg/day as well as the mean daily dose of 0.55 mg/kg were comparably low, these authors also report significantly more responders in the MPH group (61 %) than in the placebo group (42 %).

A very recent meta-analysis (Castells, Cunill, & Capella, 2013) combined the results of twelve medication studies with over 2,000 adult patients diagnosed with ADHD according to DSM-IV-TR (2000). The authors found that all MPH formulations were more effective than placebo in reducing ADHD symptoms, with some heterogeneity between studies. However, patients medicated with MPH (particularly with the OROS formulation) were more likely to discontinue treatment than patients receiving placebo. The authors also point to a potential bias of the included studies caused by possible blinding failure of the investigators due to the visible behavioural and hemodynamic effects of methylphenidate. These effects might allow trained clinical investigators to distinguish between patients receiving MPH and patients receiving placebo, even if they are formally blind to the intervention.

To summarise, double-blind placebo-controlled trials seem to indicate a superiority of MPH treatment over placebo in aADHD, both when symptom reduction and response rates are considered. There is, however, some indication that treatment effects might be more pronounced in fixed dose or forced titration trials than in more externally valid flexible dose titration trials, with the overall daily dosage in some of the studies being rather high. In addition, effects might be more visible on investigator ratings compared to patient self-reports, with the potential for blinding failures due to visible consequences of MPH treatment for the trained clinician.

1.1.3 Higher Order Cognitive Functioning

(1) Theories

Besides the well-known deficits in the regulation of activity, behavioural impulses, and attention, research interest also focused on a potential impairment of higher order cognitive functioning in ADHD. In 1997, Barkley proposed an extremely influential theory that shifted the focus away from deficient attentional processes and linked the behavioural inhibition deficit observed in the predominantly hyperactive-impulsive and the combined type ADHD to impaired executive functioning and motor control (see Figure 1.1 for a schematic of this model).

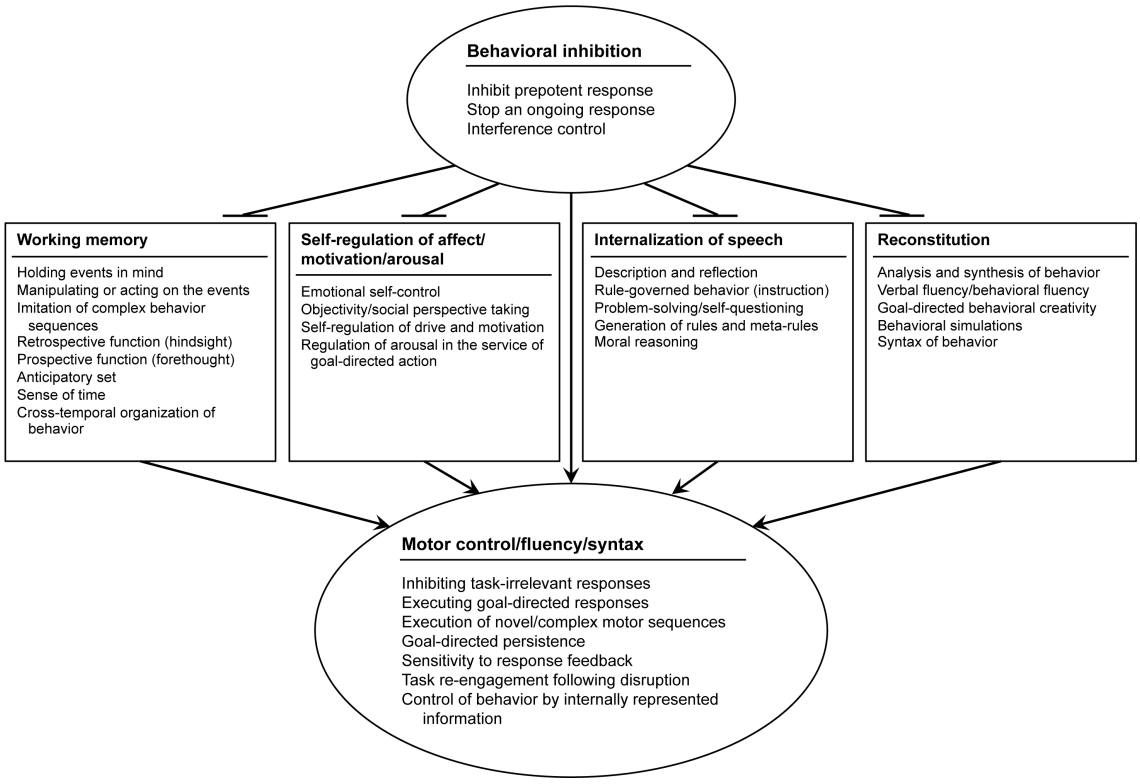

Figure 1.1: Schematic of the model linking the behavioural inhibition deficit in ADHD to impaired executive functioning and motor control (Barkley, 1997). The figure was modified from the original to improve legibility.

ADHD of the predominantly inattentive type was explicitly excluded from this model, as Barkley (1997) proposed that the attentional deficits of this subtype were related to deficient attentional focus and speed of information processing and thereby qualitatively different from the attentional deficits related to persistence and distractibility observed in the two other subtypes. Importantly, although many adults with ADHD might present with the predominantly inattentive type due to a reduction of hyperactivity with increasing age, Barkley notes that the model should still be valid for those adults suffering from ADHD of the predominantly hyperactive-impulsive or combined type in childhood.

According to this model, the core deficit in ADHD is impaired behavioural inhibition. This central deficit leads to impairment in the executive functions (EF) that rely on behavioural inhibition – working memory, self-regulation, internalised speech, and reconstitution. These EF normally act to bring behaviour under the control of internally represented information and are thus necessary for goal-directed action and task persistence, both of which are impaired in ADHD. Barkley (1997) reports empirical evidence for an impairment of behavioural inhibition and its subcomponents, of the EF of working memory and self-regulation, and of motor control, with research of internalised speech and reconstitution in ADHD being still scarce.

A meta-analysis of studies investigating EF deficits in children and adolescents with ADHD confirmed an overall impairment in the investigated EF domains of response inhibition, vigilance, set-shifting, planning/ organization, and verbal as well as spatial working memory (Willcutt, Doyle, Nigg, Faraone, & Pennington, 2005). The authors report a medium effect size across the different paradigms with lower effects for measures of set-shifting, Stroop interference control, and visuospatial attention orienting. Interestingly, there was some evidence of an association of inattention but not hyperactivity/ impulsivity with EF deficits, contradicting Barkley's (1997) assumptions and raising the possibility of the predominantly hyperactive-impulsive type as an aetiologically distinct disorder. Still, based on the much smaller effect sizes for EF dysfunction than for ADHD symptoms in the reviewed studies, the authors conclude that although EF seem to be impaired in ADHD, deficient behavioural inhibition and EF dysfunction

are “neither necessary nor sufficient to cause all cases of ADHD” (p. 1336). This result was confirmed by a meta-analysis of studies with aADHD patients (Boonstra, Oosterlaan, Sergeant, & Buitelaar, 2005). The authors found medium effect sizes for different EF tasks (verbal fluency, inhibition, set-shifting), but also for tasks classified as non-EF (response consistency, word reading, colour naming) leading them to question the assumption of EF dysfunction as an exclusive underlying cause of ADHD. A meta-analysis examining working memory research in children and adolescents with ADHD furthermore reports a significant impairment in the ADHD group compared to a control group (Martinussen, Hayden, Hogg-Johnson, & Tannock, 2005). These deficits were particularly pronounced in the areas of spatial information storage and manipulation, but were also significant for the verbal domain.

The fact that EF impairment in ADHD is clearly visible on a group level, but is not necessarily on an individual level led researchers to investigate plausible alternatives. Another very influential model was proposed by Sonuga-Barke (2005). He suggested that ADHD might result from impaired reward-related motivational processes mediated by frontoventral striatal and mesolimbic dopaminergic functioning (for a recent review see Plichta & Scheres, 2013) in addition to executive dysfunction that resulted from deficient frontodorsal striatal and mesocortical dopaminergic functioning. In a further development of this model, an abandonment of the notion of one core deficit underlying ADHD was suggested and the alternative possibility of different neurophysiological and developmental pathways leading to the same disorder was considered (Castellanos, Sonuga-Barke, Milham, & Tannock, 2006). It was proposed to distinguish between ‘cool’ EF, which were necessary to solve abstract tasks like working memory or interference control, and ‘hot’ EF needed for affectively loaded problems like delay discounting. As supported by previous research, ‘cool’ EF should be related to the inattention dimension of ADHD whereas ‘hot’ EF were hypothesised to be specific for the hyperactivity/ impulsivity dimension. In addition, while ‘cool’ EF were proposed to be linked to functioning of the dorsolateral prefrontal cortex (DLPFC) and the dorsal anterior cingulate cortex (dACC), ‘hot’ EF should be mediated by the orbital and medial PFC as well as the

ventral striatum and the nucleus accumbens. According to this model, an impairment of 'cool' and 'hot' EF can be expected on a group level, but the individual ADHD patient may show deficiencies in 'cool' EF, 'hot' EF, or both, depending on his or her symptomatology.

It has to be noted that the development of the above-described models as well as their empirical support are almost exclusively based on studies investigating children and adolescents with ADHD. However, given the stability of cognitive deficits over time, they should nevertheless also be applicable to an adult population (Castellanos et al., 2006).

(2) Neuroimaging Research

Recent neuroimaging studies succeeded to link the hypothesis of altered EF in ADHD to functional differences between aADHD patients and healthy controls during task completion. A functional magnetic resonance imaging (fMRI) study (Valera et al., 2010) investigated aADHD patients and matched healthy controls using the classic n-back task (J. D. Cohen et al., 1994). The researchers found significantly less prefrontal activation in the aADHD group than in the healthy control group in the absence of behavioural performance differences. The results also indicated more pronounced differences for male than for female participants and a differential association of task-related activation with hyperactive/ impulsive and inattentive symptomatology for men and for women. A similar fMRI study with a sample of medication-naïve aADHD patients found an overall decreased activation pattern in the task-positive network when task-related activation of the aADHD group was visually compared to a matched control group (Bayerl et al., 2010). However, the only significant between-group difference was found in the right parietal cortex. An fMRI study using a variant of the Stroop task (Stroop, 1935) also found widespread activation differences with healthy controls showing more activation than aADHD patients in DLPFC, anterior cingulate cortex (ACC), posterior parietal cortex, and right inferior frontal cortex (Banich et al., 2009).

Given the observation of altered activation patterns in patients with ADHD, research has also focused on the investigation of these patterns. An older meta-analysis of 16 neuroimaging studies in children, adolescents, and adults with ADHD used activation likelihood estimation (ALE) and identified a pattern of hypoactivation in ADHD patients compared to healthy controls (Dickstein, Bannon, Castellanos, & Milham, 2006). Patients showed significantly lower activation in the left ventral PFC and DLPFC, ACC, and bilateral parietal cortex, with significantly higher activation only in the left insular and middle frontal gyrus. These results were confirmed by a more recent meta-analysis, which used the same method to analyse 39 fMRI studies of children and adolescents with ADHD, and 16 studies of adults (Cortese et al., 2012). This meta-analysis reports hypoactivation in children with ADHD compared to controls in bilateral frontal areas and the putamen as well as in right parietal and temporal areas. Hyperactivation was found in the posterior cingulate cortex (PCC) and the midcingulate cortex. In contrast, adults with ADHD showed significant hypoactivation in the right central and precentral gyri as well as in the right middle frontal gyrus, and hyperactivation in the right angular and middle occipital gyri. This meta-analysis also tried to link the identified activation clusters to previously defined neurophysiological networks. Interestingly, children with ADHD showed most hypoactivation in the frontoparietal network, while hyperactivation was found in the default mode and somatomotor networks. The ventral attention network was associated with hypo- but to a lesser extent also with hyperactivation. In contrast, adults with ADHD showed the strongest hypoactivation in the frontoparietal network, with some hyperactivation in the visual, dorsal attention, and default mode networks. Results were similar when only studies with medication-naïve participants were considered. The authors note, however, that the lack of results for the dorsal attention network might be caused by the selection of studies, which were mostly investigating inhibition processes subserved by the ventral attention network.

In addition, a recent fMRI study showed altered connectivity in adult patients with ADHD: A complex parametric verbal working memory task that required the maintenance and manipulation of one, two, or three letters showed no behavioural performance differences between a group of aADHD patients and a

healthy control group (Wolf et al., 2009). However, during the delay period of the task, aADHD patients' connectivity in a network consisting of bilateral lateral prefrontal cortex, striatum, and cingulate cortex differed significantly from that of healthy controls with decreased connectivity in bilateral ventrolateral prefrontal, anterior cingulate, and superior parietal areas, but increased connectivity in right prefrontal, and left dorsal cingulate and occipital regions.

To summarise, the deficient EF found on a behavioural level when ADHD patients were compared to healthy controls appears to have an equivalent on a neurophysiological level as assessed with fMRI. This altered neurophysiological functioning in ADHD seems to be more visible when activation patterns instead of cluster differences are examined. Studies linking the location of observed differences to hypothesised neurophysiological network activation in aADHD showed hypoactivation in the frontoparietal network and hyperactivation in the default mode and (as a potential compensation mechanism) in the dorsal attention network.

(3) Effects of Stimulant Medication

Neuropsychological and imaging studies also investigated the impact of MPH treatment on the behavioural performance of participants with ADHD. An open-label trial of OROS MPH showed a significant improvement of test scores on the Stroop as well as on the Working Memory Index comprising the Arithmetic and Digit Span subtests of the Wechsler Adult Intelligence Scale 3rd Edition (WAIS-III) (Wechsler, 1997) in aADHD patients after 38 days of medication (Fallu, Richard, Prinzo, & Binder, 2006). In contrast, a similar placebo-controlled study of OROS MPH reports no behavioural effects on a modified version of the Stroop (Bush et al., 2008). The fMRI data, however, showed a significant interaction of group and time of scan with the MPH group displaying increased activation in the dACC as well as in the left DLPFC and bilateral parietal lobe at the second scan. A double-blind placebo-controlled single dose cross-over fMRI study investigating interference inhibition in a sample of boys with ADHD found reduced activation in

several task-related areas with MPH increasing activation in the right DLPFC and striatothalamic regions to the level found in healthy controls (Rubia et al., 2011). A similar study using a parametric n-back task found worse performance and significant hypoactivation of the bilateral DLPFC during the 2-back condition in boys with ADHD compared to healthy controls (Cubillo et al., 2013). Patients taking MPH showed higher activation of the left DPLFC during the 2-back condition, leading the authors to propose an up-regulation of the task-positive network through MPH. A naturalistic cross-over study of adolescents with ADHD examined fMRI activation during a working memory task with patients both on and off their usual stimulant medication (Wong & Stevens, 2012). The authors report increased activation in frontoparietal networks after stimulant intake as well as increased functional connectivity throughout the brain.

A very recent meta-analysis examined placebo-controlled studies which investigated the effects of MPH on behavioural EF and non-EF measures in children diagnosed with ADHD (Coghill et al., 2013). MPH was found to improve all of the examined functions, with a small effect on working memory measures requiring manipulation of the maintained material and a medium effect on working memory measures requiring simple storage and reproduction. No negative effects of MPH were found for any of the investigated measures. Interestingly, the effect sizes reported for the different cognitive domains were smaller than the effect sizes usually found in treatment studies focusing on ADHD symptom reduction. This might be the result of EF studies only recruiting patients with neuropsychological functioning within the normal range or, as described under 1.1.3 (1), it might be a further indication of the heterogeneous neuropsychological profiles found in ADHD (Coghill et al., 2013). However, this difference might also be caused by the greater objectivity of neuropsychological tests compared to the investigator or self-report ratings of ADHD symptoms normally used in treatment studies.

To conclude, behavioural studies show a robust positive effect of stimulant medication on EF as well as non-EF measures. In line with these findings, fMRI studies of working memory and interference control show increased activation particularly in the DLPFC, but also in parietal and striatal regions after the intake

of stimulant medication. Studies employing a network perspective furthermore report an upregulation of task-positive/ frontoparietal networks. It should be noted, however, that almost all of these studies rely on children or adolescents with ADHD, and that network activation patterns might change somewhat with increasing age and the accompanying decline in hyperactive behaviour (Cortese et al., 2012). In addition, there is a scarcity of investigations using placebo-controlled designs spanning several weeks, with most studies relying on dispensing single doses of medication or using a naturalistic on/off design.

1.2 The *COMT* Gene

1.2.1 Val^{158}Met Single-Nucleotide Polymorphism

In 1958, researchers described an enzyme that they called "catechol O-methyl transferase" (Axelrod & Tomchick). This enzyme could transfer a methyl group to the phenolic hydroxyl group in epinephrine as well as in other catechols. The *O*-methylation catalysed by this enzyme was hypothesized to play a major role in the metabolism of catecholamines and was later linked to the inactivation of the catecholamine neurotransmitters norepinephrine, epinephrine, and dopamine (Ball, Breuer, Haupt, & Knuppen, 1972; Guldberg & Marsden, 1975). More than one decade later, researchers found evidence for one single gene located on chromosome 22q11.1-q11.2 coding the catechol-*O*-methyltransferase (COMT) enzyme (Bertocci et al., 1991; Grossman, Emanuel, & Budarf, 1992; Lundström, Salminen, Jalanko, Savolainen, & Ulmanen, 1991). This gene comprises six exons with the third exon containing two different promoters that are responsible for initiating translation of the soluble as well as the membrane-bound form of COMT (Tenhunen et al., 1994). The membrane-bound form of COMT contains an additional 50 amino acids that are responsible for its hydrophobic properties (Lundström et al., 1991). The predominantly translated form of COMT depends greatly on the investigated tissue, with membrane-bound COMT constituting the

vast majority of all COMT enzymes found in the brain (Hong, Shu-Leong, Tao, & Lap-Ping, 1998; Tenhunen et al., 1994).

In 1995, researchers realized that two previously published human *COMT* sequences specified different amino acids (valine and methionine, respectively) at position 108 for the soluble COMT form due to a single-nucleotide polymorphism (SNP) in the responsible gene. Although this difference did not affect functionality of the resulting enzyme, the methionine (met) variant proved to be more thermolabile leading to already reduced activity at physiological temperatures of as little as 37°C (Lotta et al., 1995). Biochemical simulations showed that the substitution of valine (val) with the larger met residue caused inefficient packing of the resulting enzyme and thereby decreased enzyme stability while not impairing functionality (Rutherford, Bennion, Parson, & Daggett, 2006). The same SNP of the *COMT* gene (rs4680) exists for the membrane-bound form of the enzyme at codon 158 (val^{158}met polymorphism) (Lachman et al., 1996), with two val-alleles causing three to four times more COMT activity than two met-alleles and heterozygosis leading to intermediate activity (Chen et al., 2004; Weinshilboum, Otterness, & Szumlanski, 1999). The distribution of the two *COMT* alleles varies widely across different populations: While frequencies of the val- and met-allele are nearly equal in European populations, most African and Asian populations show a much higher frequency of the val-allele (Palmatier, Kang, & Kidd, 1999).

Due to the low expression of the DAT in the PFC, COMT plays a critical role in clearing dopamine from the synaptic cleft in this area (Dickinson & Elvevag, 2009; Lewis et al., 2001; Lewis, Sesack, Levey, & Rosenberg, 1997; Meyer-Lindenberg & Weinberger, 2006; Tunbridge, Bannerman, Sharp, & Harrison, 2004). The significance of the COMT enzyme for regulating dopaminergic transmission in the PFC therefore provides a direct link of the val^{158}met polymorphism to higher order cognitive functions. Bilder and colleagues (2004) proposed an influence of COMT on cortical as well as subcortical dopamine levels by drawing on the tonic-phasic hypothesis of dopaminergic functioning. The original tonic-phasic model, which was developed to explain symptoms of schizophrenia, held that dopaminergic transmission in subcortical regions was

regulated by tonic as well as phasic dopamine release (Grace, 1991). The phasic dopamine response is hypothesised to consist of a sudden transient release of dopamine in the striatum in response to behaviourally relevant stimuli. This dopaminergic action is then equally suddenly terminated by rapid re-uptake of dopamine from the synaptic cleft. In contrast, tonic dopamine levels are hypothesised to be mediated by glutamatergic neurons, which stimulate the continuous release of low amounts of dopamine in the striatum. These glutamatergic neurons most likely originate in the PFC as well as other cortical regions, allowing subcortical dopamine levels to be influenced by cortical processes. Tonic dopamine release is hypothesised to be much slower and more prolonged than phasic release and to mainly influence extracellular dopamine levels. Tonic dopamine levels might thus affect the responsivity of the entire dopamine system by stimulating dopamine autoreceptors which in turn control the amplitude of the phasic dopamine response (Grace, 1991).

In their refined version of this model, Bilder and colleagues (2004) stress the importance of COMT for subcortical tonic dopamine levels. Phasically released dopamine is rapidly taken up from the synaptic cleft by the DAT. However, this re-uptake process does not affect continuously released low levels of tonic dopamine, which can escape the synaptic cleft and thereby contribute to extracellular tonic dopamine levels. As hypothesised by the original model (Grace, 1991), high levels of tonic dopamine suppress the phasic dopamine response by stimulating D1 autoreceptors. According to Bilder and colleagues (2004), this is where the different versions of COMT gain importance: The highly active COMT version coded by the val-allele maintains low tonic dopamine levels thereby increasing the amplitude of phasic dopaminergic transmission. In contrast, the low active version coded by the met-allele leads to high levels of tonic dopamine thereby decreasing phasic dopamine transmission.

The impact of COMT becomes even more pronounced in the PFC where the phasically as well as the tonically released dopamine diffuses out of the synaptic cleft. In this area, carriers of two met-alleles therefore show much higher concentrations of cortical dopamine than val-allele carriers (Bilder et al., 2004). With regard to cognitive functions, the constantly increased D1 stimulation in

met/met carriers is hypothesised to lead to increased stability of neural networks underlying working memory functions, while the more transiently increased D2 stimulation in val/val carriers should support increased flexibility of these networks (Bilder et al., 2004; Levy, 2007). Met/met carriers should therefore show superior performance on "stable" working memory tasks that require maintenance processes or sustained executions of fixed response sets. In contrast, val/val carriers should be superior on "flexible" working memory tasks, e.g. tasks demanding constant updating of working memory content or switching of response sets (Bilder et al., 2004). Since the *COMT* allele is codominant (Spielman, Weinshilboum, & Opitz, 1981), val/met carriers should place intermediate on all of these variables.

1.2.2 Impact on Attention and Working Memory

The hypothesised influence of the *COMT* polymorphism on higher order cognitive functioning was previously explored in numerous studies: Egan and colleagues (2001) used the Wisconsin Card Sorting Test (WCST) as a broad measure of EF. In this test, participants have to identify the response category by which to sort an extended set of ambiguous cards (Heaton, Chelune, Talky, Kay, & Curtiss, 1993). After the participant has sorted ten consecutive cards correctly, the response category is suddenly switched without informing the participant. Performance measures usually take perseverative errors, which occur after switching of the response category, as well as the amount of trials required to obtain a stable representation of the new correct response category into account. This complex test seemed to favour met-allele carriers with the met-allele positively influencing performance in an allele dosage fashion (Egan et al., 2001). However, a recent meta-analysis pointed out that while the met-allele might indeed be associated with slightly better WCST performance, this effect was most pronounced in early studies and might therefore be overrated (Barnett, Scoriels, & Munafo, 2008; Dickinson & Elvevag, 2009). In addition, the WCST requires a wide range of mental abilities – concept formation, mental flexibility, performance monitoring, and performance adjustment – that are subsumed under the broad

term of EF but that must in fact be classified as containing stable as well as flexible working memory components (Bilder et al., 2004; Dickinson & Elvevag, 2009). Since stable and flexible task requirements are thought to differentially benefit met- and val-allele carriers, conflicting findings are to be expected (Bilder et al., 2004).

Given the ambiguous findings obtained with the WCST, researchers tried to implement a task that more clearly taxed either stable or flexible aspects of working memory, thereby allowing a priori predictions as to what allele might be favourable to overall performance. The n-back task seemed to fulfil these conditions: In its original form, this task requires participants to hold in mind several sequentially presented numbers and to indicate whenever a number is identical to the number presented "n" (usually one, two, or three) trials before (J. D. Cohen et al., 1994). A modified version of this task developed by Weinberger and colleagues (Goldberg et al., 2003) uses similar instructions but requires participants to constantly indicate the number seen "n" trials earlier, thereby increasing demands on EF while still allowing a parametric increase of working memory load. As this task requires a stable representation of the presented numbers (Goldberg & Weinberger, 2004), it was expected to favour met-allele carriers. This hypothesis was confirmed by an early study using the modified n-back paradigm: Val/val carriers gave significantly fewer correct responses than met/met carriers in both the 1-back and the 2-back condition with val/met carriers tending to perform in between (Goldberg et al., 2003). In another study, val/val carriers showed less efficient functioning of frontal areas than met/met carriers, as indicated by more fMRI activation in the absence of performance differences, with val/met carriers showing intermediate activation (Egan et al., 2001).

However, a meta-analysis of studies using the n-back task found that the val-allele was actually associated with better performance (Barnett et al., 2008), although there was evidence that this association was reversed in schizophrenic patients and results indicated a substantial heterogeneity between studies. In addition, effect sizes in the investigated samples increased with a greater number of female participants and also with increasing sample age. Still, it has to be noted

that this meta-analysis analysed studies that used different versions of the n-back task. Visual inspection of the individual results shows that the modified n-back task might actually slightly benefit met/met carriers (see Figure 1.2), which would be in line with the results of Goldberg and colleagues (2003) that are not included in this analysis.

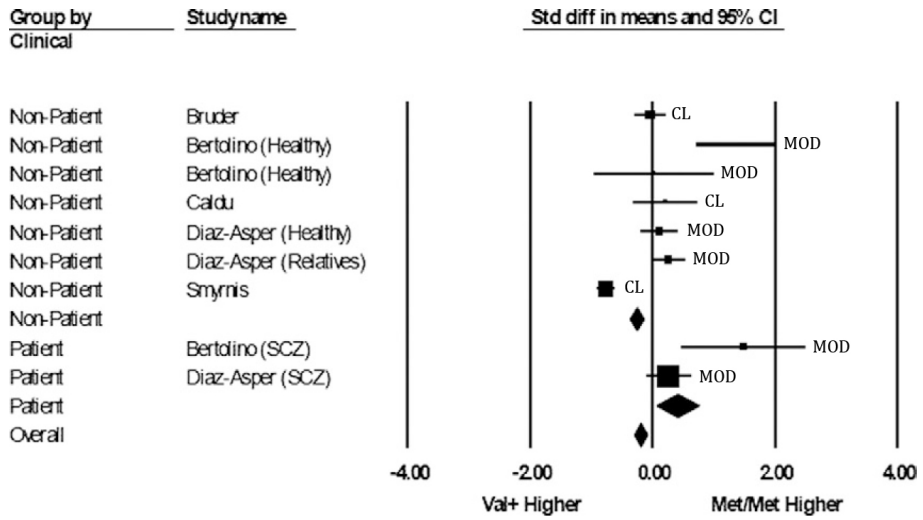

Figure 1.2: Results of the meta-analysis by Barnett and colleagues (2008). The figure was modified from the original graph to show which paradigm was used by the respective study. 'CL' denotes the classic n-back paradigm as described in Cohen et al. (1994), 'MOD' denotes the modified n-back task used by Weinberger's group (e.g. Goldberg et al., 2003).

While findings on the behavioural effects of different *COMT* alleles thus show no clear benefit of one allele over the other, the initial finding of less efficient frontal functioning in val-allele carriers reported by Egan et al. (2001) seems to be more robust. A meta-analysis of studies investigating the effect of *COMT* genotype on fMRI activation during cognitive processing found an overall greater prefrontal activation in val-allele carriers, pointing to less efficient frontal lobe functioning caused by this allele (Mier, Kirsch, & Meyer-Lindenberg, 2010). Importantly, this effect seems to persist when only the studies using the modified n-back task are considered (see Figure 1.3).

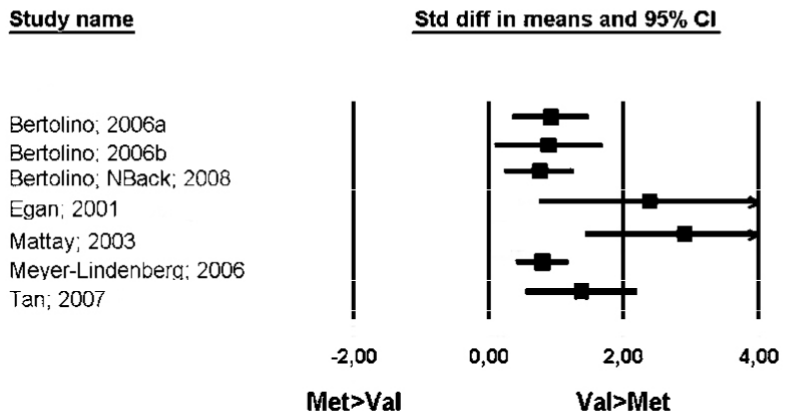

Figure 1.3: Results of the meta-analysis by Mier and colleagues (2010). The figure was modified from the original graph to show only those studies that employed the modified n-back task (e.g. Goldberg et al., 2003).

A study by Mattay and colleagues (2003) showed that efficient frontal lobe functioning was indeed connected to dopamine levels in this region, and that these levels were in turn influenced by participants' *COMT* genotype. The researchers measured frontal lobe efficiency in participants homozygous for the *COMT* genotype during the modified n-back task. Participants were given either amphetamine – a substance known to increase synaptic and extracellular dopamine levels (Schiffer et al., 2006) – or a placebo. During the simple 1-back condition, all groups showed the same level of activation in a region of interest in the left PFC. As difficulty increased, val/val participants showed less efficient frontal lobe functioning *only* after the intake of placebo. All participants who had been assigned to take amphetamine showed similar activation that was independent of their genotype. Interestingly, this pattern was reversed in the most difficult 3-back condition. Here, val/val carriers showed the least efficient activation after placebo intake, but the most efficient activation after the intake of amphetamine. The opposite was true for met/met carriers. The authors concluded that their results provide evidence for an inverted U-shaped cortical response function to dopamine in the PFC: While increased dopamine associated with the intake of amphetamine moved val/val carriers towards the peak of the function (i.e. towards optimal efficiency), met/met carriers were pushed to the far right of

the function, resulting in a decrease of cortical efficiency caused by an excess of cortical dopamine.

To conclude, while most studies investigating higher cognitive functions and *COMT* show no *behavioural* differences among the three genotypes, fMRI studies fairly consistently point to increased cortical activation in participants homozygous for the val-allele. Participants homozygous for the met-allele typically show the lowest – presumably most efficient – activation, with heterozygous participants usually located in between these two groups. Interestingly, this pattern of results can be reversed when the amount of available cortical dopamine is increased: While a pharmaceutically induced increase in cortical dopamine benefitted val/val carriers, it was actually harmful for met/met carriers, providing evidence for an association of the inverted U-shaped cortical response function to dopamine and efficient cortical activation in the PFC.

1.2.3 *COMT* Genotype and ADHD

Given the implication of *COMT* in PFC noradrenergic and dopaminergic neurotransmission and the impact of its polymorphism on higher order cognitive functioning, the *COMT* genotype was investigated as a possible candidate gene for ADHD. The high estimated heritability of ADHD of around 70 % (Faraone et al., 2005) led many studies to search for common genetic variants causing the disorder – with disappointing results. A meta-analysis of genome-wide association studies (GWAS) of almost 3,000 children with ADHD did not reveal any significant associations and the authors concluded that either several common genetic variants with extremely small contributions or not investigated rare variants like copy number variants might be involved in the aetiology of ADHD (Neale et al., 2010). Although no gene reached genome-wide significance, the most likely associated genes were found on chromosomes 7, 8, 11, and 20 with many of these genes having still unknown effects in the brain. An analysis of a priori defined candidate genes also did not yield any results with genome-wide significance.

A meta-analysis of research on candidate genes revealed significant associations of the dopaminergic genes *DAT1*, *DRD4*, and *DRD5* with childhood ADHD (Gizer, Ficks, & Waldman, 2009). Significant heterogeneity in study results was found for *DAT1*, *DRD4*, and *DRD5*, but also for the noradrenergic genes *DBH* and *ADRA2A*, which the authors interpreted as potentially indicating the investigation of dissimilar groups – like gender or ADHD subtype – who have differing genetic contributions to their ADHD symptoms. This inclusion of dissimilar subgroups in genetic analyses might furthermore be partly responsible for the overall small associations found in this study. The authors found no indication for an association of *COMT* genotype (with val being generally considered the risk allele) and ADHD, although they pointed to the slight possibility of a sexually dimorphic effect of *COMT* with met being the risk allele for boys and val being the risk allele for girls.

In addition, although a recent review gave some indication of different genes being partly responsible for ADHD in children and in adults, the authors concluded that sample sizes must still be vastly increased before GWAS studies could possibly find any significant associations (Franke et al., 2012). The authors furthermore stressed the importance of focussing research on intermediate phenotypes – so-called endophenotypes – that are classified based on neuroimaging results and neuropsychological testing. The thereby obtained "purer" samples should share more similar profiles of strength and weaknesses and thereby stronger associations with possibly responsible genetic variants than more heterogeneous samples.

Several studies investigated the impact of *COMT* genotype on neuropsychological endophenotypes in ADHD (Kebir & Joober, 2011). A study of 124 children with ADHD found no effect of *COMT* genotype on EF measures of working memory, attention, and response inhibition (Mills et al., 2004). A sample of 118 children with ADHD also showed no association of *COMT* genotype and EF tasks historically used to assess frontal lobe damage, namely the WCST, the Tower of London, and the Self-Ordered Pointing Task (Taerk et al., 2004). In contrast, a third study used a delayed-match-to-sample task and reports a negative association of val/val genotype and working memory performance in children with

ADHD (Matthews et al., 2012), while a fourth study found a negative association of the met-allele and a measure of sustained attention in ADHD children (Bellgrove et al., 2005). So far, only one study examined a sample of adults with ADHD. This study found a positive association of the val/met genotype and full-scale IQ as assessed with the WAIS-III (Boonstra et al., 2008). The authors report no main effect of *COMT* genotype on the WAIS subtests *Digit Span Forward* or *Digit Span Backward* or the Stroop *Color Word Test*. None of these studies investigated a healthy control group.

As both *COMT* genotype and MPH are thought to influence prefrontal cortical and subcortical dopamine and noradrenaline levels (Berridge et al., 2006; Bilder et al., 2004) research also focused on the question whether *COMT* genotype might influence the medication response in ADHD. Based on the assumption of an inverted U-shaped cortical response function to dopamine in the PFC (see also Mattay et al., 2003) it was hypothesised that the optimal dose of stimulant medication should vary depending on patients' *COMT* genotype with met/met patients requiring considerably lower doses than val/val patients, with val/met patients in between (Levy, 2007, 2009). This hypothesis was confirmed by a 6-month medication study of 122 children with ADHD, which classified significantly more children with val/val than with met/met genotype as responders, with val/met genotype children showing an intermediate response rate (Kereszturi et al., 2008). *COMT* genotype was also found to significantly interact with hyperactive-impulsive symptom severity, with val/val children presenting with significantly fewer symptoms than met/met children after the treatment. An 8-week trial with 128 Korean children reports similar (albeit weaker) results with val/val children's treatment response being rated as better than met/met children's in the absence of medication dose differences (Cheon, Jun, & Cho, 2008). It has to be noted, however, that the proportion of children with met/met genotype in both studies was rather low (14 and eight, respectively), somewhat limiting the conclusions that can be drawn from the obtained results. A double-blind placebo-controlled fixed-dose cross-over trial with children and adolescents reports an association of MPH response and *COMT* genotype as well (McGough et al., 2009), although only on a trend level. In contrast, a study investigating MPH response in

adults with ADHD found no indication for an association of *COMT* genotype and medication response (Contini et al., 2012). It is potentially problematic, however, that this study collapsed the data of met-allele carriers (met/met and val/met). As children with val/met genotype were previously reported to show intermediate response rates, this analysis strategy may have diluted any existing effects.

Overall, GWAS as well as candidate gene studies do not point to *COMT* as a risk gene for the development of ADHD, and studies on the neuropsychological impact of *COMT* in ADHD patients show greatly differing results that might depend heavily on the type of working memory measure used. In addition, as *COMT* becomes more important with increasing age (Barnett et al., 2008; Levy, 2007) its functional impact on PFC mediated cognitive functions may be more visible in adults than it is in children. Research on the impact of *COMT* genotype on response to treatment with stimulant medication also yielded conflicting results, with studies showing a possible association of good treatment response and the val-allele in a gene dosage fashion in children, while a study of adult patients showed no association of treatment response and the met-allele.

1.3 Working Memory

1.3.1 Theories

Nearly forty years ago, Hitch and Baddeley (1976) proposed the concept of working memory as a new system separate from short- and long-term memory, which took the form of a general executive. This executive processing system was proposed to have limited capacity and to operate as short-term storage for memory items during complex cognitive tasks. Over the years, the basic model grew increasingly refined and 16 years later, working memory was described as "a brain system that provides temporary storage and manipulation of the information necessary for […] complex cognitive tasks" (Baddeley, 1992, p. 556). Working memory was now proposed to consist of a central executive, whose main function

was to coordinate information input from and attention allocation to two visual and speech-related slave systems, the visuospatial sketch pad and the phonological loop.

Given this very influential theory, much research has focused on finding the neural correlates of working memory. In a ground-breaking study, researchers measured single-cell activity in monkeys' PFC and frontal eye fields while the monkeys performed a visual delayed-response task (Funahashi, Bruce, & Goldman-Rakic, 1989). The researchers found that many of the investigated neurons continued to exhibit directional activity changes during the delay period – in the absence of a physical stimulus – which stopped as soon as the behavioural response was executed. These results were interpreted as evidence for the DLPFC's role in working memory. However, as each neuron seemed to respond maximally to a specific spatial location, the firing was construed as a mnemonic process with each neuron possessing a so-called "memory field" where its responsiveness was highest (Goldman-Rakic, 1995).

In contrast to this view of the PFC as subserving specific memory – i.e. storage – functions, Postle (2006) proposed working memory to be an "emergent property" of the nervous system. In this model, working memory functions "emerged" whenever attention was directed to a specific kind of information that required shot-term retention. According to this theory, the brain regions originally involved in the processing of a given stimulus accomplished the short-term storage of this information. Since PFC activity was seen across a wide array of different working memory tasks, the author proposed that its activity might serve to control interference from internal and external sources, to maintain a given task-set, and/ or to provide attentional monitoring and selection during a given task. In a recent summary of his work, Baddeley (2012) similarly described the main role of the central executive as affording attentional control of action. He proposed the central executive to be especially involved in attentionally demanding working memory tasks and to focus attention in the presence of distracting stimuli as well as to divide attention if two stimuli were equally important for the task at hand. The central executive's originally assumed second role as providing short-term storage of information was moved to a separate component (the episodic buffer), which

was hypothesised to be under the control of the central executive. The main focus of the central executive was now seen in modulating attentional processes.

1.3.2 Working Memory and Selective Attention[1]

Since theoretical models of working memory started to assume an important role of selective attention for the sound functioning of working memory, much research has focused on this interface of working memory and selective attention. An influential study using a delayed recognition paradigm investigated neural activity in visual regions involved in the processing of face and house stimuli (Gazzaley, Cooney, McEvoy, Knight, & D'Esposito, 2005). The authors found a suppression of visual processing when a stimulus was not task relevant and an enhancement when it was: FMRI data showed changing activation in fusiform and parahippocampal regions of interest (ROIs) depending on task relevance. Electroencephalography (EEG) data recorded from the same participants revealed longer peak latencies and reduced peak amplitudes of an event-related potential (ERP) of early visual processing particularly sensitive to facial stimuli (N170) (Bentin, Allison, Puce, Perez, & McCarthy, 1996) when task irrelevant face stimuli were presented. In contrast, an ERP especially sensitive to spatial attention (P100) (Hillyard & Anllo-Vento, 1998; Mangun & Hillyard, 1991) was not significantly influenced. Another EEG study examined the N170 in a delayed recognition paradigm with distractors placed in between a to-be-remembered stimulus and the to-be-recognized item (Sreenivasan & Jha, 2007). This study found a greater reduction of amplitudes when a distractor was from the same category as the to-be-remembered stimulus indicating that the more similar a distractor was to a target stimulus the more its processing was suppressed.

The finding of reduced N170 amplitudes for task irrelevant face stimuli could also be generalized to a variation of the classic n-back task which presented relevant stimuli interspersed with irrelevant stimuli (Schreppel, Pauli, Ellgring,

[1] Parts of this section are published in *BMC Neuroscience* (Biehl et al., 2013).

Fallgatter, & Herrmann, 2008). This study also found enhanced N170 amplitudes for task relevant stimuli. Moreover, task relevance seemed to influence P100 amplitudes, with task relevant stimuli leading to higher amplitudes than passively viewed stimuli. This effect of task relevance on P100 amplitude was replicated in another study and seemed to be connected to working memory performance (Rutman, Clapp, Chadick, & Gazzaley, 2010).

Drawing on the models of working memory described above this processing modulation might be induced by the PFC central executive, which could modulate attention to stimuli depending on their task relevance. Egner and Hirsch (2005) point to a model originally stemming from research on error processing (J. D. Cohen, Botvinick, & Carter, 2000). This model suggests a processing system, which regulates attentional resources by drawing on two distinct components: 'conflict monitoring' and 'cognitive control'. Conflict monitoring is mediated by the ACC and serves to detect response conflict in on-going tasks. Once a conflict is detected, Cohen and colleagues (2000) propose the implication of two different processes: The first process is mediated by the ACC and affects the preparation of future responses. The second process, however, is delegated to the cognitive control system, which is located in the DLPFC and corresponds to the central executive in Baddeley's (2012) model. This control system is hypothesised to use long-range projections to visual areas to increase selective attention by influencing the processing of relevant and of distracting information.

This model has since been confirmed by findings from neuroimaging research (MacDonald, Cohen, Stenger, & Carter, 2000), and several studies investigated the involvement of frontal areas in distractor processing (for reviews see Gazzaley & Nobre, 2012; Miller & D'Esposito, 2005). Increased PFC activation was found in a delayed recognition task when only some of the presented stimuli were task relevant (Gazzaley et al., 2007), and when a distractor presented during the delay was from the same category as the to-be-remembered stimulus (Jha, Fabian, & Aguirre, 2004). Investigations of functional connectivity furthermore revealed activity correlations between visual association cortices and PFC regions if the task demanded a modulation of stimulus processing (Gazzaley et al., 2007). In addition, EEG studies investigating patients with DLPFC lesions report increased

cortical responses to task irrelevant stimuli in these patients (Barcelo, Suwazono, & Knight, 2000; Chao & Knight, 1998). Furthermore, there appears to be increased processing of irrelevant and distracting stimuli with increasing age (Boehm, Dering, & Thierry, 2011; Clapp & Gazzaley, 2012; Gazzaley et al., 2008), which has been associated with a substantial decline in prefrontal grey matter volume (Raz et al., 1997).

To summarise, there is evidence of early visual processing being influenced by the task relevance on the processed stimulus. This processing modulation is most likely induced by the allocation of selective attention to task relevant (and away from task irrelevant) stimuli. Previous research located the source of this instance of central executive or cognitive control in the PFC and there seems to be a direct association of activation in this area and the measured processing modulation based on the task relevance of a stimulus.

2 Summary and Rationale

Although studies indicate that the prevalence of ADHD in the general population declines with increasing age (de Zwaan et al., 2012; Michielsen et al., 2012), about 5 % of young adults meet full diagnostic criteria for this disorder (Willcutt, 2012). Symptoms were shown to be stable over time with about 15 % of diagnosed children still meeting full diagnostic criteria after several years and about 65 % of patients showing only partial remission (Faraone et al., 2006). This has far-reaching implications, as ADHD is consistently associated with lower educational and professional achievement as well as worse mental and physical health (Biederman, Petty, et al., 2010; Biederman et al., 2012; Brook et al., 2013; Gjervan et al., 2012). In this context, the efficient treatment of ADHD symptoms gains great importance. Studies reliably showed higher response rates and increased symptom reduction when patients were treated with MPH – a stimulant blocking the dopamine and the norepinephrine transporter and inhibiting monoamine oxidase – compared to a placebo (Castells et al., 2013).

Theories of ADHD aetiology placed a focus on impaired behavioural inhibition presumably leading to EF deficits (Barkley, 1997). In fact, EF impairment in ADHD patients is clearly visible on a group level, both for children (Willcutt et al., 2005) and for adults (Boonstra et al., 2005) with effect sizes in the medium range. Specific impairment was also found for measures of working memory (Martinussen et al., 2005), which is considered an important component of higher order cognitive functioning. Neuroimaging studies report neurophysiological findings consistent with the described behavioural impairments: Researchers investigating functional brain activity in unmedicated aADHD patients from a network perspective report hypoactivation in the frontoparietal network as well as hyperactivation in the default mode network and – as a potential compensatory mechanism – in the dorsal attention network (Cortese et al., 2012). Past treatment with stimulant medication had little effect on the observed activation patterns.

Studies investigating the acute effects of stimulant medication on EF show an improvement on behavioural EF measures including working memory manipulation and storage with small and medium effect sizes, respectively (Coghill et al., 2013). In addition, MPH was shown to up-regulate the task-positive/ frontoparietal network in children and adolescents with ADHD (Cubillo et al., 2013; Wong & Stevens, 2012). So far, only few studies investigated the impact of ADHD on behavioural and neurophysiological EF measures in adults as well as the effect of several weeks of stimulant medication in a double-blind placebo-controlled design.

The val^{158}met SNP of the *COMT* gene is a common genetic polymorphism found to have a substantial impact on subcortical and cortical dopamine and norepinephrine concentrations with met/met carriers exhibiting higher cortical neurotransmitter levels than val/met carriers and much higher levels than val/val carriers (Bilder et al., 2004; Chen et al., 2004; Weinshilboum et al., 1999). This was hypothesised to have a profound influence on higher cognitive functions where met/met carriers should benefit from working memory tasks demanding stability of neural networks and val/val carriers should benefit from tasks demanding flexibility of these networks (Bilder et al., 2004; Levy, 2007). Studies investigating the effect of this polymorphism on the behavioural performance of working memory tasks found weak indications for a possible behavioural advantage of val-allele carriers (Barnett et al., 2008). In contrast, val-allele carriers fairly consistently showed less efficient prefrontal cortical functioning when fMRI studies of working memory were considered (Mier et al., 2010). Interestingly, a pharmacological study indicated that increasing the amount of cortical dopamine (and norepinephrine) can reverse this efficiency pattern (Mattay et al., 2003): While an increase in cortical dopamine benefitted val/val carriers, it was actually harmful for met/met carriers, providing evidence for an association of the inverted U-shaped cortical response function to dopamine and efficient cortical activation in the PFC.

The importance of the COMT enzyme for subcortical and cortical dopaminergic and noradrenergic functioning led researchers to extensively investigate *COMT* as a potential candidate gene for ADHD. Contrary to

expectations, neither GWAS nor candidate gene studies found any evidence for an hypothesised increased ADHD risk transferred by the val-allele (Franke et al., 2012; Gizer et al., 2009; Neale et al., 2010). The effect of this polymorphism on higher order cognitive functioning also led to studies investigating a potential interactive impact of *COMT* genotype and ADHD on neuropsychological functioning with a particular focus on working memory (Bellgrove et al., 2005; Matthews et al., 2012; Mills et al., 2004; Taerk et al., 2004). The results of these studies are very heterogeneous, with some studies finding no interaction and others finding a disadvantage for val/val carriers or for carriers of the met-allele, likely depending on the type of working memory measure used (Matthews et al., 2012). Until now, there is only one study of adults with ADHD, which found the val/met genotype to be most beneficial (Boonstra et al., 2008). As none of these studies compared the results of ADHD patients to those of a healthy control group, a possible differential effect of *COMT* in patients compared to healthy controls might have been missed.

The three studies presented in this dissertation aimed to accomplish several goals. The first goal was to further refine an experimental paradigm hypothesised to tax selective attention mediated by the central executive component of working memory, as specified in Baddeley's (2012) model. Since neurophysiological research previously implicated the PFC as subserving central executive functions (Funahashi et al., 1989; Goldman-Rakic, 1995; Postle, 2006), we further investigated whether subclinical symptoms of aADHD and the *COMT* genotype, respectively, might have an impact on performance and neurophysiological functioning during this task. In a third study, performance and functional brain activity in aADHD patients and healthy controls during this selective attention task as well as during a standard working memory task were compared. A particular focus was placed on activity in the task-positive/ attention network. Furthermore, working memory and interference control were examined using three well-established neuropsychological tests. The impact of stimulant treatment on functional activation and behavioural performance during these tasks was investigated in a 6-week placebo-controlled double-blind clinical trial with MPH or a placebo being dispensed to the participating aADHD patients in an externally valid free titration design. Given the scarcity of previous research on this topic,

possible interactive effects of *COMT* genotype and aADHD on the above-mentioned tasks were also explored.

3 Study 1: EEG Parameters of Selective Attention[2]

3.1 Introduction

As described under 1.3.2, several studies previously focused on the contribution of central executive control to successful performance of working memory tasks that require selective attention in the face of distraction. EEG and fMRI studies employed a wide variety of paradigms with task relevant and task irrelevant stimuli from either the same or different categories, thereby varying the degree of distraction the task irrelevant stimuli produced (Gazzaley et al., 2005; Jha et al., 2004; Rutman et al., 2010; Schreppel et al., 2008; Sreenivasan & Jha, 2007; Zanto & Gazzaley, 2009). For all of these studies, relevance-induced processing differences were fairly consistent across paradigms. Most EEG studies showed peak amplitude differences for the N170, with relevance-induced peak latency differences apparently less consistent across the different paradigms. Peak amplitudes were reported to be enhanced (Schreppel et al., 2008) and/or suppressed (Gazzaley et al., 2005; Polk, Drake, Jonides, Smith, & Smith, 2008; Sreenivasan & Jha, 2007; Zanto & Gazzaley, 2009), depending on the relevance of the processed stimulus. Results regarding frontal EEG components possibly reflecting DLPFC activity are scarce and more conflicting: One study used a continuous n-back design and reports more positive amplitudes for task relevant stimuli compared to task irrelevant or passively viewed stimuli (Schreppel et al., 2008). In contrast, another study investigated the slightly different topic of recovery from interference and found significantly higher amplitudes after the presentation of a distracting stimulus than after no distraction (K. Kessler & Kiefer, 2005).

All studies, however, differed greatly in the employed paradigm, with some studies relying on simultaneous presentation of both task relevant and distracting task irrelevant stimuli (Rutman et al., 2010), while others presented task relevant and task irrelevant stimuli in sequential order (Gazzaley et al., 2005; Schreppel et

[2] Results from the following study are published in *BMC Neuroscience* (Biehl et al., 2013)

al., 2008; Sreenivasan & Jha, 2007; Zanto & Gazzaley, 2009). The thereby created conditions were also dissimilar across studies: While all studies contained task relevant stimuli, the task irrelevant stimuli differed in their degree of distraction (Sreenivasan & Jha, 2007), depending on whether the distracting stimuli were from the same or a different category as the task relevant stimuli (Gazzaley et al., 2005; Rutman et al., 2010; Schreppel et al., 2008). In addition, only some studies included a passive viewing control condition (Gazzaley et al., 2005; Rutman et al., 2010; Schreppel et al., 2008; Zanto & Gazzaley, 2009), which appears to lead to somewhat intermediate activation. No study so far included both high and low distracting task irrelevant stimuli as well as a passive viewing control condition.

In order to compare passively viewed stimuli to task relevant and to high and low distracting task irrelevant stimuli, several aspects of the above-mentioned tasks were combined: We used a modified n-back paradigm (J. D. Cohen et al., 1994) similar to the one employed by Schreppel and colleagues (2008) to investigate both P100 and N170 amplitudes, with task relevant and task irrelevant stimuli being alternately presented in sequential order. The structure of this paradigm provided by the underlying n-back task allows for the examination of continuous attentional processes, which differentiates this paradigm from previous investigations using delayed recognition paradigms. The continuous nature of this modified n-back task should be more conducive to a stable attentional set than the delayed recognition paradigm where attention necessarily fluctuates between trials. In addition, the behavioural data obtained with this paradigm can easily be related to both impulsivity (provided by the 'false alarms' parameter) and inattention (provided by the 'detected targets' parameter), which makes it especially suitable for the assessment of participants with deficits in attention regulation.

The main goal of this study was the examination of EEG activity related to the early processing of task relevant and high as well as low distracting task irrelevant stimuli, and of frontal processes related to selective attention and recovery from interference (K. Kessler & Kiefer, 2005; Schreppel et al., 2008). This task requires EF by drawing on working memory functions in the form of the central executive (selective attention) and short-term storage of information

(maintenance). Since both EF and working memory were previously found to be deficient in childhood as well as aADHD (Boonstra et al., 2005; Martinussen et al., 2005; Willcutt et al., 2005) subclinical symptoms of ADHD were assessed in order to explore whether distractor processing might vary systematically with the amount of reported ADHD symptoms.

3.2 Hypotheses

1. We expected task relevant stimuli to lead to enhanced amplitudes and high distracting task irrelevant stimuli to lead to reduced amplitudes relative to the passive viewing control condition (Gazzaley et al., 2005; Schreppel et al., 2008).
2. In line with previous studies, low distracting task irrelevant stimuli should lead to significantly less suppression and thereby higher amplitudes than high distracting task irrelevant stimuli (Sreenivasan & Jha, 2007).
3. Regarding the frontal components, we expected higher amplitudes after the presentation of high distracting task irrelevant stimuli (K. Kessler & Kiefer, 2005).
4. In addition, we hypothesised that participants with pronounced ADHD symptoms would have higher N170 amplitudes to high distracting task irrelevant stimuli – indicating increased processing because of increased distractibility – than participants with less pronounced symptoms.
5. Given the increased distractibility and hyperactivity/ impulsivity associated with ADHD and the connection of ADHD with problems of top-down distractor suppression and executive (cognitive) control (Dramsdahl, Westerhausen, Haavik, Hugdahl, & Plessen, 2011; Friedman-Hill et al., 2010), we also expected a correlation of participants' scores on three CAARS DSM-IV self-report scales and the

behavioural task performance parameters 'false alarms' and 'detected targets'.

3.3 Methods

3.3.1 Experimental Paradigm[3]

The experimental task consisted of a 1-back paradigm with alternately presented task relevant and task irrelevant stimuli. Our task employed pictures of neutral faces taken from the FERET database (Phillips, Wechsler, Huang, & Rauss, 1998) and pictures of German houses without any prominent distinguishing features. For lack of an existing database, the house pictures were taken in a rural area in southeast Germany. All pictures were edited using Adobe® Photoshop® CS4 (version 11.0, Adobe Systems, Inc., San Jose, USA) to remove any apparent distinguishing features.

The experiment consisted of three conditions: Two experimental conditions ("houses relevant" and "faces relevant") and a passive viewing control condition. Each condition was presented twice, yielding a total of six blocks containing eighty stimuli each. Of these eighty stimuli, forty (i.e. 50 % of all stimuli presented in the block) were task relevant and forty (i.e. another 50 %) were task irrelevant distractors. For the two experimental conditions, the forty relevant stimuli were all from the same category (i.e. 100 % "face" or 100 % "house" stimuli). In contrast, the forty task irrelevant stimuli were split evenly to be from the same category as the task relevant stimuli (yielding twenty high distracting stimuli, i.e. 50 % of all task irrelevant stimuli were high distracting) or from another category (yielding twenty low distracting stimuli, i.e. 50 % of all task irrelevant stimuli were low distracting). The passive viewing control condition always contained forty house

[3] Portions of the research in this study use the FERET database of facial images collected under the FERET programme.

stimuli (i.e. 50 % of all presented stimuli) and forty face stimuli (i.e. another 50 %), which – only in this condition – were presented in random order.

During each "houses relevant" and "faces relevant" condition, five task relevant stimuli (i.e. 12.5 % of all task relevant stimuli presented in the block) were repeated in a 1-back fashion requiring a behavioural response. Three task relevant stimuli (i.e. 7.5 % of all task relevant stimuli) were repeated in a 2-back fashion not requiring a behavioural response. The 2-back repetitions were included to ensure that participants would not simply react to the familiarity of a stimulus. All repeated stimuli were excluded from later EEG data analysis. On a behavioural level, reaction times for correct responses as well as number of false alarms and number of detected target stimuli were recorded. Every picture was shown only once in one of the three conditions. Task irrelevant stimuli never required a behavioural response.

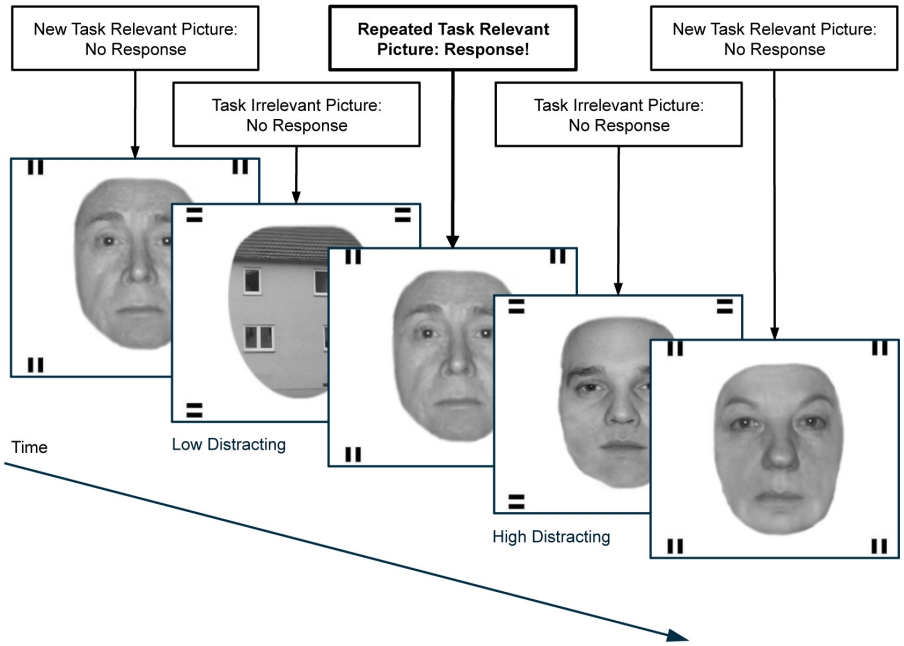

Figure 3.1: The experimental paradigm. Vertical bars mark task relevant stimuli; horizontal bars mark task irrelevant stimuli. Participants were supposed to indicate when a task relevant picture was repeated 1-back while ignoring the interspersed task irrelevant distractors.

Although task relevant and task irrelevant stimuli were presented alternately, the task relevance or task irrelevance of a stimulus was additionally

indicated by two horizontal or vertical bars in each of the four corners of the display (see Figure 3.1 for an example of the "faces relevant" condition). Participants were instructed beforehand about the markings (e.g. horizontal bars marking task relevant stimuli and vertical bars marking task irrelevant stimuli – this was counterbalanced across participants) and markings were kept consistent across the entire experiment. All stimuli were presented for 1,000 ms with the interstimulus interval showing a grey fixation cross and ranging from 1,750 ms to 2,750 ms. This experimental set-up led to four different relevance-levels of the presented stimuli: task relevant stimuli, high distracting task irrelevant stimuli, low distracting task irrelevant stimuli, and passively viewed stimuli. Participants were seated 50 cm from the monitor and viewed stimuli of approximately 10 cm height by 7.5 cm width. The whole display including the markings was 12 cm by 12 cm, subtending 14° of visual angle.

3.3.2 Participants

Fifty participants took part in this study. They were recruited from a previously established subject pool (see also Gschwendtner et al., 2012) as well as through university advertisement. Participants were mostly students and received 12€ as compensation for their participation. All participants were right-handed, had normal or corrected-to-normal vision, and were free of neurological or psychiatric diseases. However, due to a technical mistake, a substantial part of the data was recorded with an erroneous filter, not allowing the implementation of the required high-pass filter of 0.1 Hz during data analysis. Therefore, only forty per cent of the original sample (twenty participants) could be fully analysed (see Table 3.1 for ADHD symptoms, depressive symptoms and affectivity of that sample). Ethical approval was obtained through the Ethical Review Board of the medical faculty of the University of Würzburg; all procedures involved were in accordance with the 2008 Declaration of Helsinki. Participants gave written informed consent after full explanation of procedures.

Table 3.1: Mean (SD) of demographic data, CAARS DSM-IV ADHD symptoms, BDI-II depressive symptoms, and PANAS affectivity for the analysed sample.

Age (years)	25.4(*4.1*)	*Men/ women*	5/15
CAARS (T-scores)		*PANAS*	
Inattentive Symptoms	43.6(*8.9*)	Positive affect	19.7(*6.3*)
Hyperactive/Imp. Symptoms	42.1(*9.7*)	Negative affect	2.7(*4.4*)
Total ADHD Symptoms	42.0(10.3)	*BDI-II (sum score)*	6.2(*6.7*)

3.3.3 Psychological Assessment

Participants completed three ADHD questionnaires to assess individual symptoms of both childhood and adult ADHD: The Adult ADHD Self-Report Scale (ASRS) (R. C. Kessler et al., 2005) is an 18-item questionnaire assessing ADHD symptoms based on the DSM-IV-TR (2000). Participants were pre-screened and selected based on their ASRS scores to ensure variability of ADHD symptoms in the sample. All participants had either a score of ten or lower on both the inattention and the hyperactivity/ impulsivity scale or a score of at least 15 on any one of the two scales. The CAARS (Conners et al., 1999) is a more refined questionnaire, adding symptoms of aADHD to the core ADHD symptoms (Christiansen et al., 2012; Christiansen et al., 2011). To ensure that no participant met full diagnostic criteria of childhood ADHD as described in the DSM-IV-TR (2000), participants also completed the Wender Utah Rating Scale (WURS) (Ward, Wender, & Reimherr, 1993). No participant scored above the cut-off score for the short version (Retz-Junginger et al., 2002) of this questionnaire. To control for affect and depressive symptoms, subjects furthermore completed the Positive and Negative Affect Schedule (PANAS) (Krohne, Egloff, Kohlmann, & Tausch, 1996; Watson, Clark, & Tellegen, 1988) and the Beck Depression Inventory (BDI-II) (Hautzinger, Keller, & Kühner, 2006).

3.3.4 Electrophysiological Recording and Data Analysis

ERPs were recorded from 28 Ag/AgCl active electrodes, which were placed according to the 10-20 guidelines (Jasper, 1958) using the actiCap system (see Figure 3.2). Additional electrodes were placed under the right eye as well as on both outer canthi to monitor eye movement. The ground electrode was placed at AFz. Impedance was kept below 10 kΩ for all electrodes. Data was recorded with the software Brain Vision Recorder 1.20 (Brain Products GmbH, Munich, Germany) in relation to a midline reference electrode placed at FCz with a sampling rate of 1000 Hz.

The data was analysed with the software BrainVision Analyzer 1 (Brain Products GmbH). Band-pass filters were set to 0.1-30 Hz, with a 50 Hz notch filter. Eye movement artefacts were corrected (Gratton, Coles, & Donchin, 1983) and the data was re-referenced to an average recorded reference. Stimulus-locked EEG epochs from –100 ms to 500 ms were segmented for the different stimuli. All stimuli used for 1- or 2-back repetitions as well as segments containing false alarm responses were excluded from further analysis. The data was baseline corrected to the mean amplitude from –100 ms to 0 ms. Epochs containing artefacts with the voltage in any channel exceeding ±100 µV or showing drops or rises of more than 100 µV/ms were rejected and the remaining artefact-free epochs were averaged.

Based on the literature (Bentin et al., 1996; K. Kessler & Kiefer, 2005; Rossion & Jacques, 2008; Schreppel et al., 2008; Sreenivasan & Jha, 2007) and on grand average topography, channels O1 and O2 were selected for P100 analysis, channels P7/P8 and PO9/PO10 were chosen for analysis of the N170, and channels T7/T8 and F7/F8 were chosen for the analysis of the frontal components (see Figure 3.2).

Based on the grand average time course over all participants, the P100 was defined as the most positive peak in the time window from 70 ms to 140 ms. The N170 was defined as the most negative peak in the time window from 140 ms to 210 ms. Since the fixation cross appeared after 1000 ms of stimulus presentation and the effects of this visual stimulation change might be different across conditions, frontal components were exported as mean activity only in the time

window from 800 ms to 1000 ms. Peaks were automatically detected and manually adjusted if necessary. Peak amplitudes were then exported for subsequent analysis with SPSS Statistics 20 (IBM®, New York, USA).

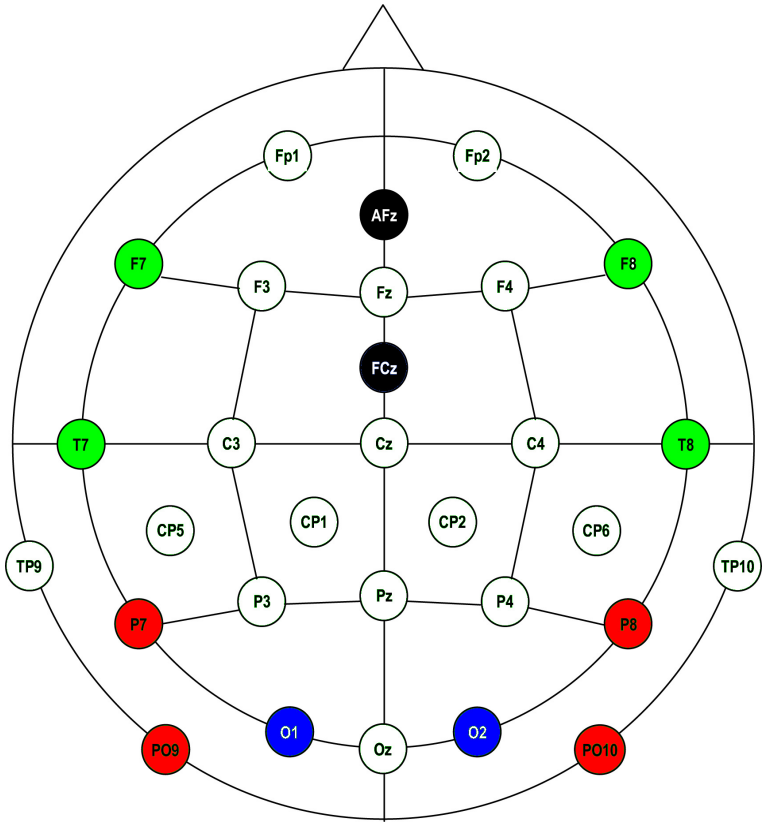

Figure 3.2: Standard layout of the actiCap 32 channel system (the active electrodes used to record eye movement are not shown here). Channels used for P100 analysis are marked blue, channels used for N170 analysis are marked red, and channels used for the analysis of the frontal components are marked green.

3.3.5 Statistical Analysis

For the behavioural data, the percentage of correctly identified target stimuli (hits) and the number of false alarms were compared for the two categories (face and house stimuli) using paired sample t-tests. In addition, an accuracy index incorporating both correct (non-)responses and false alarm

responses as described by Grimm et al. (2012) was calculated for the two categories.

ERP amplitudes were analysed separately for the P100, the N170, and the frontal components by using a repeated measures analysis of variance (ANOVA). The ANOVA for the P100 comprised the within-subjects factors *hemisphere* (left, right), *stimulus category* (face, house), and *task relevance* (relevant, irrelevant – high distracting, irrelevant – low distracting, passively viewed). The ANOVA for the N170 and the ANOVA for the frontal components included the within-subjects factors *hemisphere* (left, right), *channel group* (P7/P8, PO9/PO10 and T7/T8, F7/F8, respectively), *stimulus category* (face, house), and *task relevance* (task relevant, task irrelevant – high distracting, task irrelevant – low distracting, passively viewed). Hypotheses-driven one-sided t-tests were used for the factors *task relevance* and *stimulus category*; two-tailed t-tests were used for all other post-hoc comparisons. To control for multiple comparisons, all post-hoc t-tests were Šidák-corrected. If assumptions of sphericity were violated, degrees of freedom were adjusted according to Greenhouse-Geisser (Greenhouse & Geisser, 1959). However, to facilitate understanding only full degrees of freedom are reported below.

In addition, the following correlation coefficients were calculated: The N170 components for the four task conditions (task relevant, task irrelevant – high distracting, task irrelevant – low distracting, passively viewed) were correlated with the three CAARS DSM-IV subscales 'Inattentive Symptoms', 'Hyperactive/ Impulsive Symptoms', and 'Total ADHD Symptoms'. The N170 difference amplitude of task relevant minus high distracting task irrelevant stimuli was correlated with the same three CAARS subscales as well as with the behavioural measures 'percentage of detected targets' and 'number of false alarms', and with mean frontal amplitudes. The behavioural measures were also correlated with the three above-mentioned CAARS subscales. For all analyses, *p*-values of $\alpha \leq .05$ were considered significant.

3.4 Results

(1) Behavioural Data

All participants detected at least 50 % of the target trials. The average rate of detected targets was 88.8 % (*SD* = 9.9), the average reaction time was 741 ms (*SD* = 123; see Table 3.2 for further performance characteristics). The rates of correctly identified target trials and of false alarms as well as the average reaction time and the accuracy index were not significantly different for face versus house stimuli (all $p > .1$).

Table 3.2: Overview of mean per cent hits, reaction time, false alarms, accuracy index, and usable EEG epochs for the different conditions in the selective attention task. The standard deviation is noted in parentheses.

Behavioural data		*Number of usable epochs*	
% hits	88.8(*9.9*)	Task relevant stimuli[2]	120.3(*9.2*)
Reaction time[1]	741(*123*)	Task irrelevant, high distracting[3]	77.6(*4.7*)
False alarms	5.4(*3.5*)	Task irrelevant, low distracting[3]	77.1(*6.4*)
Accuracy index	.98(*.01*)	Passive viewing[2]	78.4(*3.4*)

Note. [1] Reaction time is reported in milliseconds (ms); [2] out of 128 epochs; [3] out of 80 epochs;

(2) EEG Data

P100

The repeated measures ANOVA with the factors *hemisphere*, *stimulus category*, and *task relevance* yielded a significant main effect of stimulus category ($F_{(1,19)} = 7.2$, $p = .02$), with significantly higher amplitudes for face compared to house stimuli. The ANOVA showed no further significant main effects or interactions.

N170

The repeated measures ANOVA with the factors *hemisphere*, *channel group*, *stimulus category*, and *task relevance* yielded a significant main effect of task relevance ($F_{(3,57)} = 9.1$, $p < .001$; see Figure 3.3 for time courses and topographies in the different conditions).

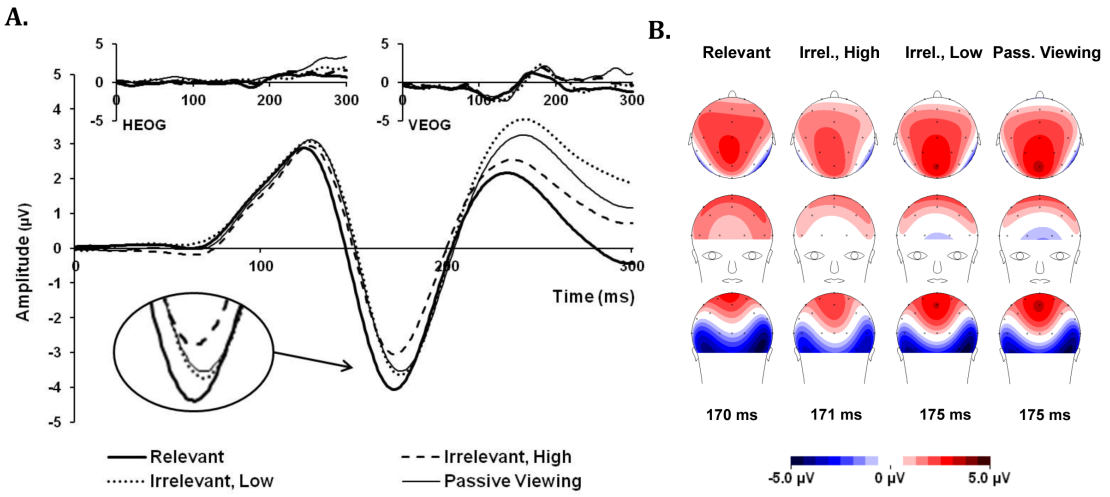

Figure 3.3: N170 grand average time courses over electrodes P7/P8 and PO9/PO10 (A.), and N170 topographies for the different conditions (B.). Horizontal (HEOG) and vertical (VEOG) electrooculogram activity is displayed in the upper part of the figure showing that eye movements were insignificant and did not differ across conditions. Topographies are shown for the grand average peak in each condition.

Across the channel groups, task relevant stimuli led to significantly higher peak amplitudes than high distracting task irrelevant stimuli ($p < .001$) and significantly higher peak amplitudes than passively viewed stimuli ($p = .03$). Low distracting task irrelevant stimuli yielded significantly higher amplitudes than high distracting task irrelevant stimuli ($p = .03$), but the amplitudes were not significantly different from task relevant stimuli ($p = .28$) and from passively viewed stimuli ($p = .36$). Amplitudes for high distracting task irrelevant stimuli and for passively viewed stimuli were also not significantly different ($p = .12$; see Figure 3.4).

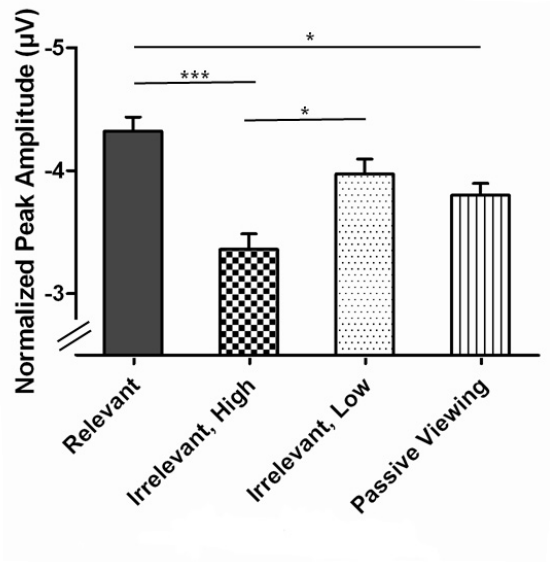

Figure 3.4: Mean N170 peak amplitudes for the different conditions. For the graph, data were normalised using the normalisation method described in Franz and Loftus (2012)[4] to remove irrelevant between-subjects differences. Error bars denote standard error of the mean for the normalised scores (SEM^{norm}).

In addition, there was a significant main effect of stimulus category ($F_{(1,19)} = 213.5$, $p < .001$) with face stimuli yielding significantly higher amplitudes than house stimuli across all channels and conditions. A significant interaction of hemisphere and channel group yielded no significant post-hoc differences. There was no significant interaction of channel group and task relevance ($F_{(3,57)} = 2.5$, $p = .07$) or of stimulus category and task relevance ($F_{(3,57)} = 2.4$, $p = .08$).

The N170 difference amplitude of task relevant minus high distracting task irrelevant stimuli was significantly correlated with the accuracy index that takes correct (non-)responses as well as false alarm responses into account ($r_{(18)} = -.56$, $p = .01$): The smaller the difference between the amplitudes (i.e. the less processing suppression for high distracting task irrelevant stimuli compared to task relevant stimuli), the lower overall accuracy (see Figure 3.5).

[4] This method first normalises the data for all subjects without changing the pattern of the effects. Since irrelevant between-subjects differences are thereby removed, the standard error of measurement is then calculated as in between-subjects designs. For a more detailed description of this method see Franz and Loftus (2012).

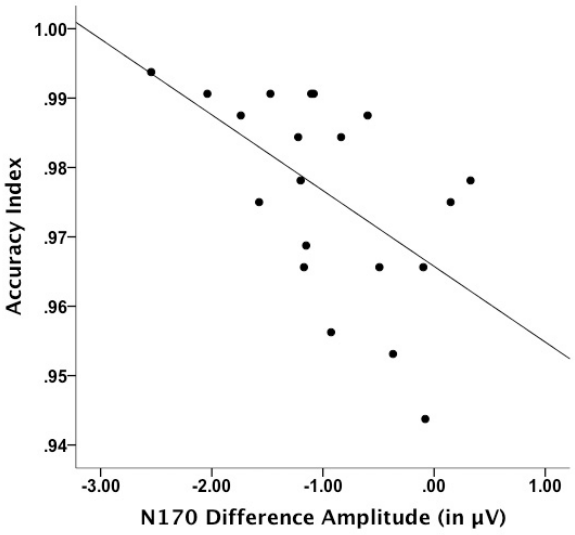

Figure 3.5: Scatter plot and linear regression line for accuracy index and N170 difference amplitude. Each dot represents one participant.

In addition, N170 amplitudes for low distracting task irrelevant stimuli as well as for passively viewed stimuli were significantly correlated with the CAARS DSM-IV Hyperactive/ Impulsive Symptoms subscale (low distracting: $r_{(18)} = .55$, $p = .01$; passively viewed: $r_{(18)} = .53$, $p = .02$) and the CAARS DSM-IV Total ADHD Symptoms subscale (low distracting: $r_{(18)} = .51$, $p = .02$; passively viewed: $r_{(18)} = .48$, $p = .03$). The more symptoms participants reported on these subscales, the lower their N170 amplitudes in these conditions. In addition, the accuracy index was significantly correlated with both the CAARS DSM-IV Hyperactive/ Impulsive Symptoms subscale ($r_{(18)} = -.46$, $p = .04$) and CAARS DSM-IV Total ADHD Symptoms subscale ($r_{(18)} = -.45$, $p = .047$). The more symptoms participants reported on these scales, the lower their accuracy indices. An examination of the individual components forming the accuracy index showed that this was likely caused by participants with high symptom detecting fewer targets than participants with lower symptoms (CAARS DSM-IV Hyperactive/ Impulsive Symptoms and percentage of detected targets: $r_{(18)} = -.52$, $p = .02$; CAARS DSM-IV Total ADHD Symptoms subscale and percentage of detected targets: $r_{(18)} = -.48$, $p = .03$).

Frontal Components

The repeated measures ANOVA with the within-subjects factors *hemisphere*, *channel group*, *stimulus category*, and *task relevance* yielded a significant main effect of task relevance ($F_{(3,57)} = 8.65$, $p = .001$) and a main effect of channel group ($F_{(1,19)} = 12.51$, $p = .002$). In addition, there was a significant interaction of channel group and stimulus category ($F_{(1,19)} = 7.58$, $p = .01$), with T-electrodes ($p = .04$) but not F-electrodes ($p = .38$) measuring more negative amplitudes for face stimuli compared to house stimuli. Because of a significant interaction of task relevance and channel group ($F_{(3,57)} = 9.69$, $p < .001$), post-hoc repeated measures ANOVAs with the within-subjects factor *relevance* were calculated separately for each channel group: For the T-channel group, there was a trend level main effect of task relevance on mean amplitudes ($F_{(3,57)} = 2.84$, $p = .054$; see Figure 3.6). Post-hoc t-tests revealed significantly higher mean amplitudes for high distracting task irrelevant stimuli compared to task relevant stimuli ($p = .02$) and compared to passively viewed stimuli ($p = .046$). Amplitudes for high and low distracting task irrelevant stimuli were not significantly different ($p = .35$).

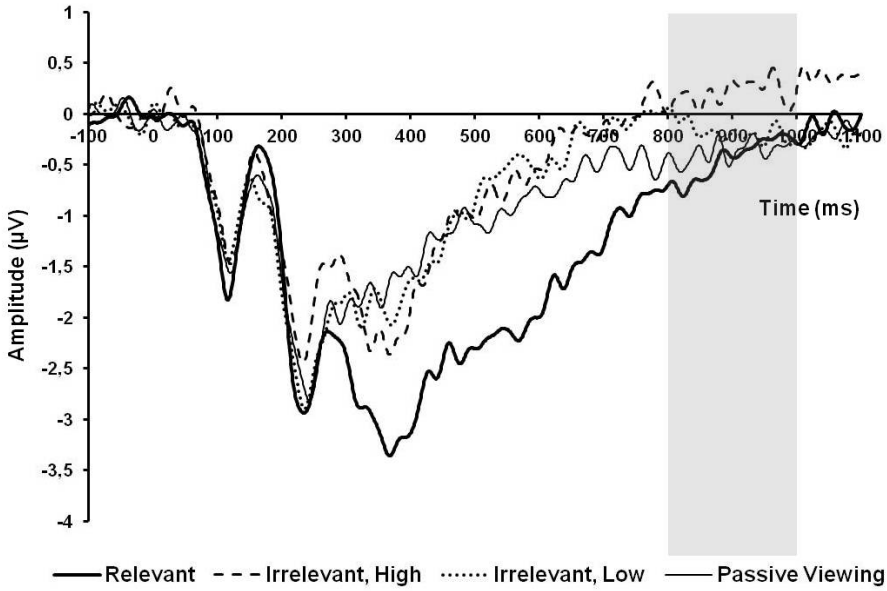

Figure 3.6: Grand average time courses over electrodes T7/T8 for the different conditions. The grey shaded area marks the time window of the analysed mean amplitudes. High distracting task irrelevant stimuli led to significantly higher mean amplitudes than task relevant stimuli and than passively viewed stimuli.

For the F-channel group, there was a significant main effect of task relevance on mean amplitudes ($F_{(3,57)} = 10.90$, $p < .001$; see Figure 3.7). Post-hoc t-tests revealed significantly lower mean amplitudes for task relevant stimuli than for high distracting task irrelevant stimuli ($p < .001$), for low distracting task irrelevant stimuli ($p = .04$), and for passively viewed stimuli ($p = .008$). In addition, high distracting task irrelevant stimuli showed a trend for higher mean amplitudes than passively viewed stimuli ($p = .051$).

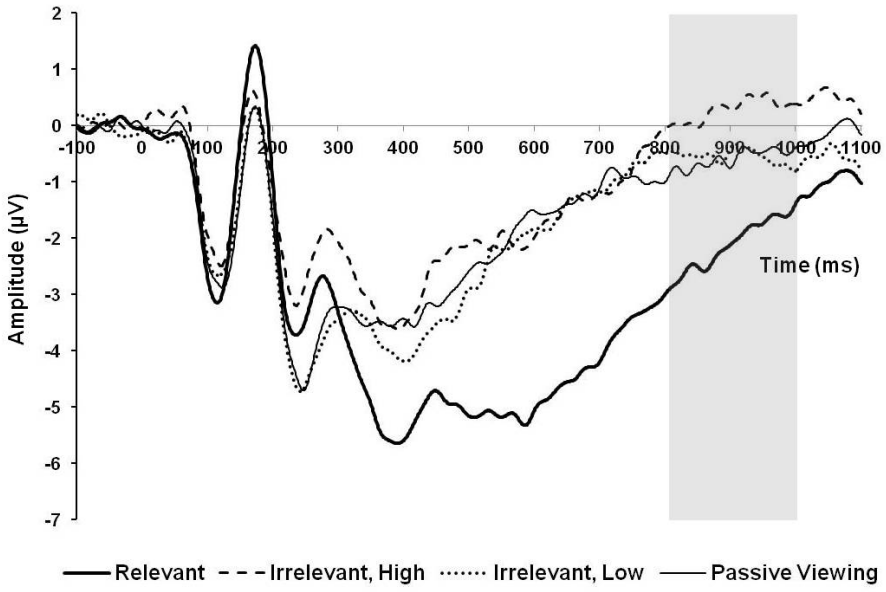

Figure 3.7: Grand average time courses over electrodes F7/F8 for the different conditions. The grey shaded area marks the time window of the analysed mean amplitudes. Task relevant stimuli led to significantly lower mean amplitudes than all other stimuli and high distracting task irrelevant stimuli showed a trend for higher mean amplitudes than passively viewed stimuli.

In addition, mean frontal amplitudes across all channels and conditions correlated significantly with N170 suppression efficiency (i.e. the difference amplitude of task relevant minus high distracting task irrelevant stimuli): The higher overall mean frontal amplitudes, the lower the suppression for high distracting task irrelevant stimuli compared to task relevant stimuli ($r_{(18)} = .45$, $p = .048$).

3.5 Discussion

We found a modulation of N170 amplitudes by the task relevance of the presented stimuli. Since our paradigm enabled us to vary the degree of distraction caused by the task irrelevant stimuli, we found an interesting dissociation that clearly extends previous findings: Peak amplitudes were significantly higher for task relevant than for high distracting task irrelevant and for passively viewed stimuli, while there was no difference for task relevant and low distracting task irrelevant stimuli. In addition, peak amplitudes for low distracting task irrelevant stimuli were significantly higher than for high distracting task irrelevant stimuli. At the same time, peak amplitudes for all distracting task irrelevant stimuli were not different from peak amplitudes for passively viewed stimuli. Amplitudes of the P100, however, were not significantly influenced by stimulus relevance.

Our pattern of results for the N170 points to a processing enhancement for task relevant stimuli compared to a passive viewing baseline. This enhancement seemed to be absent for low distracting task irrelevant stimuli, which did not differ from passively viewed stimuli. For the processing of high distracting stimuli, however, there seemed to be an additional processing suppression, as amplitudes for these stimuli were significantly lower than for low distracting stimuli. Visual inspection of the grand average waveforms suggests that the processing of high distracting stimuli might even have been suppressed below the passive viewing baseline, and the post-hoc t-test revealed that this suppression was indeed significant but did not pass correction for multiple testing.

The suppression of processing for high distracting task irrelevant stimuli compared to task relevant stimuli appeared to be directly related to task performance: Small N170 difference amplitudes for these stimuli – indicating less effective suppression – correlated negatively with an accuracy index that takes both correct (non-)responses and false alarm responses into account. Participants with less effective processing suppression were possibly more distracted by the task irrelevant stimuli, which then interfered with successful working memory maintenance of the task relevant 1-back picture and led to less accurate performance. In fact, a paired t-test yielded significantly higher mean amplitudes

for task irrelevant stimuli followed by false alarms than for task irrelevant stimuli not followed by false alarms. Although only few trials could be entered into this analysis because the number of false alarms across participants was rather low, this difference could support two different explanations: Either the processing of the distracting stimuli was generally suppressed, and when it was not participants were distracted enough to make a false alarm response to the following task relevant stimulus. Or the processing of these task irrelevant stimuli was "accidentally" enhanced, which made these stimuli more distracting and then caused false alarms later on.

The pattern found for the frontal components points to a role of the DLPFC in processing suppression and/or enhancement. While Schreppel et al. (2008) found an enhancement of frontal processing for task relevant stimuli, we found enhanced frontal processing for (high) distracting task irrelevant stimuli. Our results are in line with the findings of Kessler et al. (2005), who found enhanced frontal amplitudes at around 1000 ms after the presentation of high distracting (interfering) stimuli during a working memory task. This enhancement of frontal activity was interpreted as the DLPFC trying to recover the memory trace of the originally maintained stimulus after a high interfering task irrelevant stimulus had been presented. This interpretation could be transferred to our working memory paradigm with the distracting task irrelevant stimulus disrupting and interfering with the maintenance of the task relevant stimulus, leading to increased DLPFC activity and thereby enhanced frontal EEG components. Interestingly, mean frontal amplitudes across both investigated electrode pairs and all conditions correlated significantly with N170 suppression efficiency. Higher mean amplitudes were associated with less efficient suppression of high distracting task irrelevant stimuli compared to task relevant stimuli. This finding is difficult to interpret and might indicate a role of the observed low frontal activity during the processing of task relevant stimuli for overall processing modulation. It has to be noted, however, that the analysed time window was quite restricted, since we chose not to analyse any frontal EEG data acquired after the end of the presented stimulus and the onset of the fixation cross. In addition, the frontal electrodes entered into the analysis are not identical to the ones selected by previous studies (K. Kessler &

Kiefer, 2005; Schreppel et al., 2008) and are more posterior and more dorsal, respectively. They might thus not optimally reflect task-related DLPFC activity. Nevertheless, we found some indication that the DLPFC central executive might be involved in the processing modulation of the high distracting task irrelevant stimuli and the task relevant stimuli.

However, another possible explanation for the lower amplitudes to high distracting stimuli might be that each high distracting stimulus had to compete for processing resources with the task relevant stimulus that was being maintained in working memory. Several studies showed that simultaneous presentation of stimuli that activate the same neural populations led to decreased ERPs for the stimuli that were not directly task relevant (Ranganath & Paller, 1999; Rossion, Kung, & Tarr, 2004). In addition, the ERPs to task relevant target stimuli were found to be reduced when working memory load was increased from maintaining one face to maintaining two or more faces (Morgan, Klein, Boehm, Shapiro, & Linden, 2008). Since task relevant and high distracting task irrelevant stimuli in our study were from the same category, they likely activated the same neural networks, which might have caused the high distracting stimuli to evoke lower event-related potentials. However, stimuli in our study were subsequently (and not simultaneously) presented and working memory load consisted of only one task relevant stimulus at a time.

Another possible explanation for the increased N170 amplitudes to task relevant stimuli might be the need for stimulus discrimination when viewing these stimuli. Discriminating between stimuli has been shown to increase the posterior N1 (Vogel & Luck, 2000). Since discriminative demands in our task were high, this might have influenced the obtained amplitudes. In addition, since task relevant and task irrelevant stimuli alternated in our paradigm, it was possible for participants to know in advance if the next stimulus would be relevant or irrelevant for successful task performance. This temporal expectation might have led participants to modulate their attention before the task irrelevant stimulus was actually presented. The enhanced amplitudes to task relevant stimuli might therefore represent the effect of a more general attentional modulation induced by the structure of stimulus presentation instead of a specific effect of selective

attention. This does not, however, explain the modulation observed for the task irrelevant stimuli. Amplitudes differed significantly depending on how distracting a task irrelevant stimulus was to successful task performance. Since the degree of distractibility of the task irrelevant stimuli varied randomly across trials, selective attention processes must indeed have induced this modulation.

We furthermore found significant correlations of CAARS DSM-IV Hyperactive/ Impulsive Symptoms and Total ADHD Symptoms scores with N170 amplitudes for low distracting task irrelevant stimuli and for passively viewed stimuli, which are difficult to explain. It is important to remember that all participants were highly functioning and without clinical impairments in daily life. One possibility to interpret these correlations is therefore that participants with higher symptoms might have been more easily bored by the less demanding task conditions, leading to lower amplitudes during the presentation of passively viewed and low distracting task irrelevant stimuli. In contrast, these participants might have been able to maintain focus during the more demanding conditions (task relevant and high distracting task irrelevant stimuli), which is why no correlations were found for these conditions. However, the task still appears to tap some ADHD symptoms that cannot clearly be connected to the investigated EEG components, as increased ADHD symptoms were associated with a less accurate behavioural performance, in particular with a lower amount of detected target trials. One possible additional limitation of this study is that the passive viewing control condition might have been less arousing than the experimental conditions which might have impacted on N170 amplitudes (Egner & Gruzelier, 2001, 2004; Fekete, Pitowsky, Grinvald, & Omer, 2009; Howells, Stein, & Russell, 2010), although Vogel and Luck (2000) did not find increased arousal to enhance posterior N1 amplitudes.

In addition to replicating previous studies that showed early visual processing enhancement of task relevant and suppression of task irrelevant stimuli, this study could extend and clarify these findings. The results point to an enhancement of early visual processing of task relevant stimuli and to a suppression of task irrelevant stimuli – if these stimuli are high distracting to successful task completion. The efficiency of this processing modulation

furthermore seemed to have direct behavioural consequences. In addition, the investigation of frontal EEG components showed a potential involvement of the DLPFC in the processing of high distracting task irrelevant and of task relevant stimuli. The connection of the different EEG components to symptoms of ADHD, however, did not yield the hypothesised results, possibly because overall ADHD symptomatology in the investigated sample was rather low.

4 Study 2: fMRI Parameters of Selective Attention

4.1 Introduction

The main goal of the first (EEG) study was to test the refined version of a previously used experimental paradigm (Schreppel et al., 2008) that taxed selective attention properties of the central executive component of Baddeley's (2012) working memory model. The study could successfully replicate N170 amplitude differences for task relevant versus distracting task irrelevant stimuli (Gazzaley et al., 2005; Schreppel et al., 2008) and for high distracting versus low distracting task irrelevant stimuli (Sreenivasan & Jha, 2007). In addition, a modulation of frontal components linked to DLPFC functioning (K. Kessler & Kiefer, 2005; Schreppel et al., 2008) was found. The ability of the EEG to show DLPFC functioning, however, is limited by the inverse problem (Helmholtz, 1853; Michel et al., 2004), which does not allow definitive statements about the origin of a measured scalp potential. Therefore, the second study now aimed to transfer this experimental paradigm to fMRI.

Previous studies already used fMRI to investigate the impact of task relevance on stimulus processing as well as the potential involvement of frontal areas during these tasks (see also 1.3.2.). A study using a delayed recognition task investigated early visual processing in pre-specified ROIs during stimulus encoding and found a suppression of activation during the processing of distracting task irrelevant stimuli and an enhancement of activation during the processing task relevant stimuli relative to a passive viewing control condition (Gazzaley et al., 2005). Another study also used a delayed recognition task, but presented high and low distracting task irrelevant stimuli from the same or a different category as the to-be-remembered stimulus during the delay (Jha et al., 2004). The authors found increased left PFC activity during the delay if high distracting compared to low distracting task irrelevant stimuli were presented. In addition, activation in the fusiform face area (FFA) during the delay was increased if the task relevant as well as the distracting stimulus were faces. This increase in activation could be interpreted as increased maintenance efforts during

distraction, but it could also be construed as the additional processing of distracting faces while a task relevant face was already being maintained in working memory. However, it has to be noted that this increased activation was visible only for correct trials, supporting the potential role of increased maintenance-related activation in successful working memory performance.

Further analyses of the data set discussed above (Gazzaley et al., 2005) also showed increased activation in the left DLPFC in the encoding period, during which participants viewed task relevant and task irrelevant stimuli compared to a passive viewing control condition (Gazzaley et al., 2007). The authors also performed a functional connectivity analysis using a seed region in the left scene-selective visual association cortex of the parahippocampal gyrus that had shown the most robust effects of top-down modulation in the previous analyses (Gazzaley et al., 2005). They found a significant correlation of activation in the left parahippocampal gyrus and in the left PFC, with increased correlation when stimuli were task relevant and decreased correlation when stimuli were task irrelevant, relative to the passive viewing condition. The authors furthermore found that connectivity correlated significantly with the amount of relevance-induced processing modulation in the parahippocampal gyrus.

As mentioned above, the first goal of this study was the transfer of the experimental paradigm established in the previous EEG study to fMRI. This transfer necessitated some changes to the experimental paradigm described in 3.3.1, which were mainly related to stimulus timing. FMRI relies on the blood oxygenation level-dependent (BOLD) response. This is based on the fact that increased blood flow caused by neuronal activation leads to decreased concentrations of deoxygenated haemoglobin and that oxygenated and deoxygenated haemoglobin have differential magnetic properties, allowing the inference of neuronal activity from recorded changes in haemoglobin oxygenation (Hu, Le, & Ugurbil, 1997). The BOLD signal has been hypothesised to reflect “the input and intracortical processing of a given area” (Logothetis, Pauls, Augath, Trinath, & Oeltermann, 2001, p.150) and was found to be related to local field potentials. The temporal resolution of the BOLD signal is rather low, with an initial dip followed by a signal increase after two to three seconds and the peak response

after eight to fifteen seconds (Hu et al., 1997; Logothetis, Guggenberger, Peled, & Pauls, 1999; Logothetis et al., 2001; Malonek & Grinvald, 1996). This delayed response puts restraints on stimulus timing in experimental paradigms, although studies suggest that interstimulus intervals of 2.5 seconds might be possible for random designs with two conditions and a repetition time (TR) of two seconds, meaning that trials of the same condition would – on average – be five seconds apart from each other (Wager & Nichols, 2003).

As a second goal, the continuous nature of our paradigm should allow a replication of Jha et al.'s (2004) results of increased left PFC and FFA activation during the presentation of high distracting task irrelevant stimuli, as their delayed recognition task also involved the sequential presentation of task relevant and distracting task irrelevant stimuli spanning several seconds. A further goal of this study was to investigate the impact of the *COMT* val^{158}met polymorphism on the hypothesised elicited prefrontal activation during this task. As described in 1.2.2, this polymorphism was consistently linked to efficiency of prefrontal functional activation during working memory tasks, with met/met carriers showing less activation at equal behavioural performance levels and thereby presumably more efficient functioning than val/val carriers (Egan et al., 2001; Mattay et al., 2003; Mier et al., 2010).

4.2 Hypotheses

1. We expected high distracting task irrelevant stimuli to lead to increased activation in the PFC as well as in ROIs related to the visual stimulus processing when compared to activation for task relevant stimuli (Gazzaley et al., 2005; Jha et al., 2004).
2. In line with previous results, the task-related increase in PFC activation should be particularly pronounced in the left hemisphere (Gazzaley et al., 2007; Jha et al., 2004).

3. In addition, we hypothesised that task-induced prefrontal cortex activation would correlate with suppression efficiency in the visual ROIs (Gazzaley et al., 2007).
4. Regarding the *COMT* genotype, we expected val/val carriers to show increased activation in prefrontal ROIs indicating less efficient functioning than met/met carriers (Egan et al., 2001; Mattay et al., 2003).
5. Behavioural performance between the two genotype groups should not be different (Barnett et al., 2008).

4.3 Methods

4.3.1 Experimental Paradigm

As the goal of this study was the transfer of the experimental paradigm established in the EEG study (see 3.3.1 for a description of this paradigm) to fMRI, the task parameters remained unchanged. However, given the low temporal resolution of fMRI (see 3.1) compared to EEG, interstimulus intervals were increased and now lasted 2,500 ms to 4,500 ms. In addition, 8 scans at the beginning of the paradigm were included to allow for saturation of the signal and to serve as a baseline, respectively. Task duration was about 34 minutes, during which 673 fMRI volumes were acquired.

Since this study aimed to investigate frontal contributions to processing modulation as well as the processing modulation itself, a functional localiser was included to enable an analysis of individual ROIs in the FFA and in the parahippocampal place area (PPA). This localiser consisted of twelve 20-second blocks, during which either 20 pictures of faces, 20 pictures of houses, or a fixation cross were presented. Each picture was presented for 750 ms with 250 ms interstimulus interval. Participants were instructed to look at all pictures attentively. The total duration of this localiser was about five minutes, allowing for the acquisition of 97 fMRI volumes.

4.3.2 Participants

Twenty-six subjects (14 men) participated in this study. Participants were mostly students and were recruited from a previously established subject pool (see also Biehl et al., 2013; Gschwendtner et al., 2012) to be homozygous for the *COMT* genotype. All subjects were right-handed, with normal or corrected-to-normal vision and free of neurological or psychiatric diseases. Ethical approval was obtained through the Ethical Review Board of the medical faculty of the University of Würzburg; all procedures involved were in accordance with the 2008 Declaration of Helsinki. Participants gave written informed consent after full explanation of the procedures.

Five subjects had to be excluded due to hardware and software problems, respectively. Two subjects were excluded because they identified less than 40 % of target trials and their understanding of the experimental task was therefore doubtful. One subject was excluded after data preprocessing because of excessive movement in the scanner (sudden movement of more than 2 mm), so that the final sample included 18 participants (see Table 4.1 for sample characteristics).

Table 4.1: Overview of mean demographic data for both COMT groups. Standard deviation is noted in parentheses unless stated otherwise.

	met/met	val/val
Selective attention task		
Participants (male)	9 (4)	9 (3)
Mean age	22.3(*2.4*)	23.6(*4.4*)
Mean school years	12.7(*1.0*)	12.7(*1.0*)
MWST IQ estimate	112.4(*10.7*)	117.6(*15.2*)
Mean inattention[1]	12.2(*3.6*)	13.9(*5.5*)
Mean hyperactivity	8.9(*4.7*)*	13.2(*3.7*)*

Note. [1] Symptoms of inattention and hyperactivity/ impulsivity as assessed with the ASRS; * denotes significant between-group differences ($p < .05$); there were no between-group differences on the questionnaires not listed here (all $p > .1$).

4.3.3 Psychological Assessment

As in the previous EEG study, participants completed three ADHD questionnaires to assess individual symptoms of both childhood and adult ADHD: The ASRS (R. C. Kessler et al., 2005), the CAARS (Christiansen et al., 2012; Christiansen et al., 2011; Conners et al., 1999), and the WURS (Ward et al., 1993). To control for affect and depressive symptoms, subjects furthermore completed the Positive and Negative Affect Schedule (PANAS) (Krohne et al., 1996; Watson et al., 1988) and the Beck Depression Inventory (BDI-II) (Hautzinger et al., 2006). In addition, participants completed the Mehrfachwahl-Wortschatz-Intelligenztest (MWT-B), a short verbal screening measure that estimates IQ (Blaha & Pater, 1979).

4.3.4 fMRI Data Acquisition and Analysis

Imaging data were acquired at the Research Center for Magnetic-Resonance-Bavaria (MRB) in Würzburg using a Siemens MAGNETOM® Avanto MRI scanner with a magnetic field strength of 1.5 Tesla (Siemens AG, Erlangen, Germany) and a twelve channel head coil. The TR of the T2*-weighted gradient echo planar imaging (EPI) sequence was three seconds; the echo time (TE) was 50 ms. Further parameters were flip angle 90°, in-plane resolution 4 ×4 mm^2, field of view (FOV) 255 ×255 mm^2. One TR allowed for the interleaved acquisition of 32 axial slices of 4 mm thickness in ascending order (no gap between slices). Slice acquisition was aligned to be parallel to the AC-PC line, which runs along the anterior and the posterior commissure. The first three volumes of each sequence were discarded to allow for signal saturation. In addition, a high-resolution structural MPRAGE scan was obtained for each participant with the following parameters: TR 1870 ms, TE 3.74 ms, flip angle 15°, in-plane resolution 1.4 ×1 mm^2, FOV 250 ×250 mm^2, slice thickness 1 mm. The experimental task was presented via MRI compatible goggles (VisuaStim Digital, Resonance Technologies, Inc., Northridge, USA) using Presentation® (version 11.3, Neurobehavioral Systems, Inc., Albany, USA). In order to minimize head movement, participants lay

on a polyurethane foam head cushion with additional movement restraints mounted to the sides of the head coil.

All fMRI data were analysed with Statistical Parametric Mapping (SPM) 8 (Wellcome Trust, 2009), which uses a voxel based approach (2007; spm, 2013). In this software, a general linear model in combination with a temporal convolution model is used to describe the obtained fMRI data and hypotheses are tested using statistical inference with correction for multiple comparisons based on continuous random field theory. For all fMRI studies described in this thesis, EPI images were realigned to correct for movement during scanning and the MPRAGE scan was co-registered to the mean EPI image and segmented into grey and white matter as well as cerebrospinal fluid. These parameters were then applied to the EPI images, which were normalized to 3 mm^3 voxel size and smoothed with a 9 mm^3 full-width at half maximum (FWHM) Gaussian smoothing kernel. Subsequently, stimulus onsets were extracted from participants' logfiles and first level analyses were computed for each participant incorporating the conditions of interest as well as the movement parameters obtained during data preprocessing. Contrasts of interest were calculated for every participant and further analysed using second level analyses as specified below. Results were whole-brain FWE (family-wise error) corrected with $p < .05$ unless specified otherwise. The extent threshold for a given cluster was set at a minimum of five voxels. Peak voxels were anatomically located using WFU PickAtlas Toolbox version 2.4 (Maldjian, Laurienti, Kraft, & Burdette, 2003).

For this study, a whole brain analysis was carried out across all participants by performing a one-sample t-test with $p_{FWE} < .05$ for the contrasts of interest. Further analyses were then carried out by using two-sample t-tests as implemented in SPM8 to test for differences between *COMT* met/met carriers and val/val carriers using small volume correction (spheres with 9 mm radius placed around the MNI transformed coordinates of the peak voxels specified by Mattay et al., 2003). For all analyses, peak voxels with $p_{FWE} \leq .05$ were considered significant and peak voxels with $p_{FWE} \leq .1$ were considered trends. If the small volume correction showed a significant between-group difference or trend for a peak voxel of a given cluster, the contrast estimates of this cluster were exported for each

participant using Region of Interest Extraction (REX) Toolbox (Whitfield-Gabrieli, 2009). These mean cluster activations were then entered into SPSS Statistics 20 (IBM®, New York, USA) for further analysis[5]. For illustration purposes, the fMRI data below are rendered using MRIcron (Rorden, 2010) by overlaying the clusters on a template with 16mm search depth.

In addition, individual activation of the FFA for high and for low distracting task irrelevant face stimuli minus the face stimuli from the passive viewing control condition as well as for task relevant face stimuli minus the face stimuli from the passive viewing condition was extracted using REX Toolbox (Whitfield-Gabrieli, 2009). Furthermore, individual activation of a cluster in the left middle frontal gyrus (MFG) was extracted for high distracting task irrelevant faces minus task relevant faces. The FFA was determined in each participant by examining the individual first-level results of the contrast 'faces minus houses' from the functional localiser (see 4.3.1 for a description of this localiser). Anatomical masks of the left and the right fusiform gyrus, respectively, were overlaid over the first-level results. The significance threshold was adjusted individually in order to yield a maximally activated contiguous cluster of 10 voxels in either the right or the left fusiform gyrus for each participant. Unfortunately, the activation yielded by the house stimuli in the functional localiser was not consistent enough to analyse task-induced PPA activation in the same way.

4.3.5 Statistical Analysis

For the behavioural data, the percentage of correctly identified target stimuli (hits), the number of false alarms, reaction time, and overall accuracy were entered into separate mixed model ANOVAs with the between-subjects factor *COMT genotype* (val/val, met/met) and the within-subjects factor *stimulus category* (face, house). For the fMRI data, two-sample t-tests with *COMT* genotype as the between-subjects factor were used to compare the exported mean cluster

[5] Mean cluster activation was used for further analyses as a more robust measure of regional activation.

activations. FFA activation was analysed using a mixed model ANOVA with the between-subjects factor *COMT genotype* (met/met versus val/val) and the within-subjects factor *task relevance* (task relevant, high distracting task irrelevant, low distracting task irrelevant). Hypotheses-driven one-sided t-tests were used for the factor *task relevance*, two-tailed t-tests were used for all other post-hoc comparisons. To control for multiple comparisons, all post-hoc t-tests were Šidák-corrected. If assumptions of sphericity were violated, degrees of freedom were adjusted according to Greenhouse-Geisser (Greenhouse & Geisser, 1959). However, to facilitate understanding only full degrees of freedom are reported. In addition, correlations between cluster activations and performance data were computed. For these analyses, *p*-values of $\alpha \leq .05$ were considered significant.

4.4 Results

(1) Behavioural Data

Mixed model ANOVAs with the between-subjects factor *COMT genotype* and the within-subjects factor *stimulus category* for the percentage of hits, the number of false alarms, reaction time, and overall accuracy showed no significant main effect of *COMT* genotype or stimulus category nor a significant interaction of the two factors for any of the investigated parameters (all $p > .1$). Both groups had an overall accuracy index of around .98 and detected around 80 % of the target trials with an average reaction time of around 800 ms while committing around 4 false alarms (see Table 4.2 for the performance parameters of the two groups).

Table 4.2: Overview of mean performance for met/met carriers and val/val carriers in the selective attention task. The standard deviation is noted in parentheses.

	met/met	val/val
Selective attention task		
% hits	84.9(*10.4*)	81.3(*12.2*)
Reaction time[1]	777(*140*)	847(*154*)
False alarms	4.1(*2.9*)	4.1(*2.1*)
Accuracy index	.98(*.01*)	.98(*.01*)

Note. [1] Reaction time is reported in milliseconds (ms). There were no significant between-group differences (all $p > .1$).

(2) fMRI Data

Based on the results of the EEG study the contrast of high distracting task irrelevant stimuli minus task relevant stimuli was examined, as high distracting task irrelevant stimuli were hypothesised to be most taxing on the central executive and should thereby yield the highest DLPFC activation. Whole brain FWE-corrected data showed significantly more activation in the left precuneus, the left MFG, the right superior frontal gyrus (SFG), the left inferior parietal lobule, and the left superior temporal gyrus for this contrast. Based on the literature (Gazzaley et al., 2007) the cluster in the left MFG/DLPFC was chosen as a ROI that was potentially involved in the modulation of visual processing, and individual activation for high distracting task irrelevant minus task relevant faces in this region was extracted for each participant. Since an additional goal of this pilot study was to detect activation foci caused by the experimental paradigm, fMRI data were also examined with a significance threshold of $p < .0001$ (uncorrected). This analysis showed significant activation in the structures mentioned above as well as in the right middle and inferior frontal gyri, the bilateral fusiform gyrus, the right inferior parietal lobule, the left superior parietal gyrus, the left middle occipital gyrus, and the right superior occipital gyrus (see Figure 4.1).

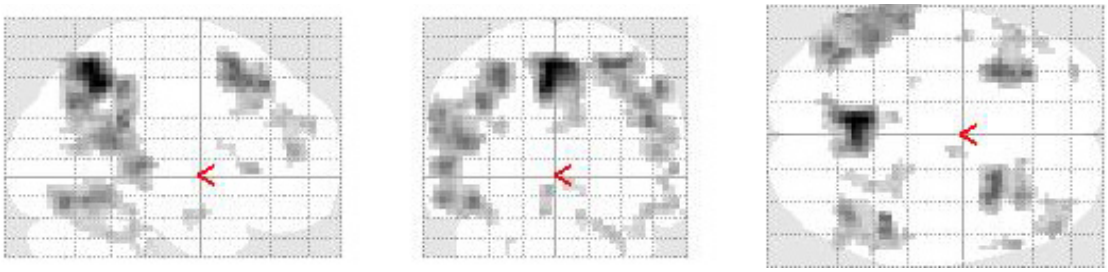

Figure 4.1: Significant voxels found in the whole brain analysis with $p < .0001$ (unc., five voxels extent threshold) for the contrast high distracting task irrelevant stimuli minus task relevant stimuli across all participants. Clusters of activation can be seen in frontal and parietal areas as well as in the bilateral fusiform gyrus.

Comparisons between *COMT* met/met carriers and val/val carriers showed no significant whole brain differences. However, ROI analyses yielded a significant peak voxel difference for one of the three examined coordinates specified by Mattay and colleagues (2003): Val/val carriers showed significantly higher activation than met/met carriers in the right medial frontal gyrus ($t_{(16)} = 3.87$, $p_{FWE} = .03$, cluster size: 28 voxels; see Figure 4.2)[6].

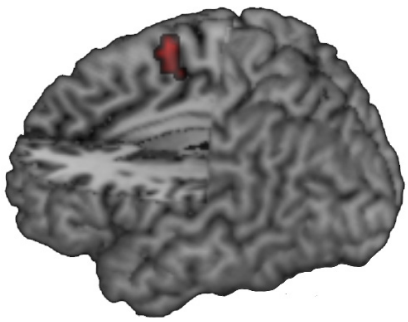

Figure 4.2: Cluster found in the ROI analyses with significantly greater peak voxel activation for the contrast high distracting task irrelevant minus task relevant stimuli in the val/val group compared to the met/met group in the right medial frontal gyrus.

A two sample t-test of the contrast estimates for the entire cluster also yielded a significant between-group difference with val/val carriers showing significantly greater activation than met/met carriers ($t_{(16)} = 3.05$, $p = .01$; met/met: $M = -0.22$, $SD = 0.42$; val/val: $M = 0.70$, $SD = 0.80$). Correlations of the

[6] See Table 8.1 (appendix) for MNI coordinates of the significant between-group peak voxel difference.

contrast estimates for this cluster showed no association of mean activity with any of the performance parameters.

Given the bilateral activation of the fusiform gyrus across all participants, individually determined activation of each participant's FFA was extracted for task relevant faces minus the passive viewing control condition, high distracting task irrelevant faces minus the passive viewing control condition, and low distracting task irrelevant faces minus the passive viewing control condition. A mixed model ANOVA with the between-subjects factor *COMT genotype* and the within-subjects factor *task relevance* yielded a significant main effect of task relevance ($F_{(2,32)} = 4.35$, $p = .02$; see Figure 4.3) with high distracting task irrelevant faces leading to significantly higher mean contrast estimates than task relevant faces ($p = .01$). Low distracting task irrelevant faces showed intermediate activation, not being significantly different from either task relevant ($p = .14$) or high distracting task irrelevant faces ($p = .33$).

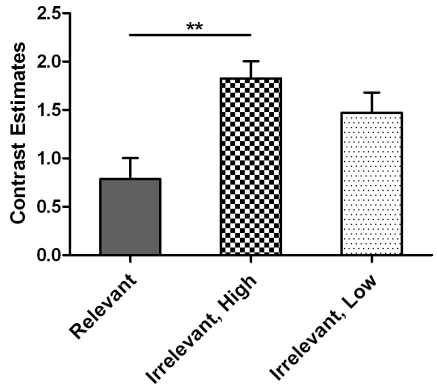

Figure 4.3: Mean FFA contrast estimates for face stimuli in the different conditions minus the passive viewing condition. For the graph, data were normalised using the normalisation method described in Franz and Loftus (2012) to remove irrelevant between-subjects differences. Error bars denote standard error of the mean for the normalised data (SEM^{norm}).

There was no significant main effect of group and no significant interaction of group and task relevance (both $p > .1$), and there were no significant correlations of mean FFA contrast estimates and any of the performance parameters (all $p > .1$). In addition, there was no correlation between left MFG activation for high distracting task irrelevant minus task relevant faces and FFA activation for the same contrast.

4.5 Discussion

The main goal of this study was to transfer the experimental paradigm established in the first (EEG) study to fMRI. Although stimulus timing had to be adjusted to accommodate for the lower temporal resolution afforded by fMRI, this transfer was generally successful and produced an analysable data set.

As expected based on previous studies (Gazzaley et al., 2007; Jha et al., 2004) our task produced robust activation in the left MFG/DLPFC when high distracting task irrelevant and task relevant stimuli were compared. In addition, activation could be found in left parietal and temporal as well as in right frontal areas, which is also consistent with previous results (Gazzaley et al., 2007). Furthermore, existing problems of previous paradigms could be avoided: Gazzaley et al.'s (2005; 2007) experimental paradigm presented two task relevant and two low distracting task irrelevant stimuli within four seconds. For this reason, all analyses had to be conducted on the combined task relevant and task irrelevant stimuli, and it was not possible to disentangle the activation caused by either stimulus class. In contrast, the continuous design of our study allowed us to contrast task relevant and high distracting task irrelevant stimuli, thereby disentangling activation related to the encoding of task relevant stimuli and to the suppression of distracting task irrelevant stimuli.

Our design furthermore enabled us to compare the obtained results to those reported by Jha et al. (2004). Although the underlying task was different, this study could contrast task relevant and high distracting task irrelevant stimuli as well. It also reports increased activation in the left PFC, although in a possibly more ventral area. In addition, we could replicate their finding of increased FFA activation during high distracting compared to low distracting task irrelevant stimuli. While FFA activation in our study was higher for high distracting task irrelevant stimuli compared to task relevant stimuli, activation for low distracting task irrelevant stimuli was intermediate and not significantly different from either of the other two stimulus classes. This finding is in line with and extends previous reports (Jha et al., 2004). In these reports, the increased activation during the presentation of high distracting task irrelevant stimuli could signify either

inhibitory processes or increased maintenance efforts during high distraction or a combination of both. However, it could also just reflect the additive effect of processing a distracting stimulus, with a stimulus from the same category that activated the same neural population already being maintained in working memory (Ranganath & Paller, 1999; Rossion et al., 2004). Our paradigm allowed us to replicate these results, but we could also further extend the findings of Jha et al. (2004) by showing increased activation for the low distracting task irrelevant stimuli, which were from another category than the maintained task relevant stimuli. This supports the interpretation of increased activation as possibly reflecting inhibitory processes in the face of distraction. However, while the low distracting task irrelevant stimuli in our study showed intermediate activation, this activation was not significantly different from the activation for both task relevant and high distracting task irrelevant stimuli. Furthermore, our paradigm did not include a "pure" maintenance condition, thereby limiting the conclusions that can be drawn from these results. Nevertheless, this finding for the FFA mimics the results from the EEG study, where low distracting task irrelevant stimuli elicited intermediate N170 amplitudes when compared to high distracting task irrelevant and task relevant stimuli. Unfortunately, a comparable analysis, which might have clarified the FFA findings, was not possible for PPA activation, as the functional localiser failed to elicit the necessary consistent PPA activation across participants.

Unlike hypothesised this study did not show an association of FFA activation and activation of a cluster in the left MFG that was assumed to be most likely responsible for producing task-induced modulation in stimulus processing. It has to be pointed out, however, that while Gazzaley et al. (2007) found activation of a similar cluster when they examined task-related activity in a univariate analysis, the reported correlations were only visible when the connectivity indices of this region and visual association areas were correlated with task-induced processing suppression. As we did not analyse connectivity between these areas, our lack of a significant association is not entirely surprising. In addition, as the DLPFC was previously found to possess greatly differentiated responsivity (Goldman-Rakic, 1995), it is possible that the MFG cluster in our study was simply

not subserving modulatory functions leading to processing consequences in the FFA.

A further goal of this study was to investigate the impact of *COMT* genotype on behavioural performance and on the elicited prefrontal activation. Since past reports of worse performance of val/val carriers compared to met/met carriers analysed very large samples and found only small to moderate effect sizes (Diaz-Asper et al., 2008), the finding of no behavioural performance differences for the two *COMT* groups was expected and is also in line with previous studies (Barnett et al., 2008; Egan et al., 2001). It has to be noted that performance data in this study indicated high performance accuracy with a target detection rate of around 80 % indicating that the task was sufficiently difficult to prevent participants from performing at ceiling level. With regard to the functional activation elicited by the task, we could replicate some of the previous findings (Egan et al., 2001; Mattay et al., 2003; Mier et al., 2010) with significantly higher activation of val/val carriers compared to met/met carriers in one of three examined ROIs in the frontal cortex. The task thus apparently taxes some of the frontal lobe functions vulnerable to activation efficiency differences caused by the *COMT* genotype, although to a lesser extent than expected. While previous studies used the modified n-back task up to a difficulty level of 3-back (Mattay et al., 2003), the high performance accuracy in our study possibly indicates that this task might not have been difficult enough to produce the necessary effort for observing frontal efficiency differences.

To conclude, our experimental paradigm enabled us to replicate previous results linked to both the processing of (high) distracting task irrelevant stimuli and to the impact of the *COMT* genotype. In addition to yielding frontal activation consistent with the literature, whole-brain results furthermore showed widespread frontal and parietal activation when results were examined with a more liberal statistical threshold, making this paradigm suited for further investigations using fMRI.

5 Study 3: Double-Blind Placebo-Controlled Trial

5.1 Introduction

This third study comprised a medium-sized sample of unmedicated aADHD patients and matched healthy controls, whose performance on a variety of tasks was compared. In addition, the study included a double-blind placebo-controlled clinical trial of MPH versus placebo for the participating aADHD patients (study code: W004PS0108_1, EudraCT: 2008-006242-26). This study therefore pursued several goals: First, as all participants completed three different neuropsychological tests, the performance of aADHD patients compared to a matched control group and the possible impact of *COMT* genotype on this performance was investigated. In addition, the effect of MPH medication versus placebo in the patients was evaluated by examining their performance at the beginning and at the end of the clinical trial.

As previous studies have shown the feasibility of transferring investigations from participants with subclinical ADHD symptoms to patient samples (e.g. Herrmann et al., 2010; Herrmann et al., 2009), a second focus of this study was the assessment of behavioural performance and functional brain activation in aADHD patients and healthy controls during the selective attention task. In addition, a possible effect of MPH medication on these parameters in aADHD patients was examined. The first (EEG) study provided some indication of subclinical ADHD symptoms impacting on processing modulation as well as on target detection rates and performance accuracy. The performance profiles of aADHD patients compared to the sample with subclinical symptoms should be similar but potentially more strongly impaired. We therefore expected to replicate and extend our previous findings from the selective attention task with the sample of aADHD patients compared to a matched healthy control group.

The third goal of this study was the investigation of the effects of a more classic working memory paradigm in aADHD patients and healthy controls as well as the examination of the impact of MPH on the investigated parameters in aADHD patients. While the selective attention task showed good results for the

investigation of the central executive component of working memory, the design of the task did not allow the investigation of more global working memory functioning. Although a meta-analysis found some indication for EF deficits in aADHD (Boonstra et al., 2005), functional imaging studies of working memory in aADHD patients are still scarce with most of the existing studies focusing on behaviour inhibition as the EF of interest (Cortese et al., 2012). One of the few existing studies that investigated adults with ADHD using the classic n-back task reports an overall decreased activation pattern in the attention/ task-positive network. Although this decreased activation was evident when task-related activation of the aADHD group was compared to a matched control group, only few significant differences were found in the whole-brain between-group comparison (Bayerl et al., 2010). Furthermore, the meta-analysis mentioned above (Cortese et al., 2012) reports hypoactivation in the frontoparietal network in adults with ADHD, with some hyperactivation in the visual, dorsal attention, and default mode networks. However, the lack of results for the dorsal attention network might be caused by most studies investigating inhibition processes subserved by the ventral attention network instead of working memory.

So far, there are no studies investigating the effects of six weeks of MPH versus placebo medication on the activation of these networks in aADHD patients using a measure of working memory. However, a placebo-controlled clinical study of aADHD patients using a modified version of the Stroop reports increased left DLPFC and bilateral parietal lobe activation after six weeks of MPH medication (Bush et al., 2008). In addition, working memory studies with children and adolescents found a down-regulation of the task-negative/ default mode network and an up-regulation of the task-positive network/ frontoparietal network through MPH (Cubillo et al., 2013; Wong & Stevens, 2012). Importantly, there is a lack of investigations using placebo-controlled designs that span several weeks, with most studies investigating children and adolescents and relying on dispensing single doses of medication or using a naturalistic on/off design.

To investigate working memory functioning in general, we decided to employ the modified n-back task. The classic n-back task was previously shown to be sensitive for functional activation differences in both children and adults with

ADHD compared to healthy controls as well as for stimulant medication effects (Kobel et al., 2009; Valera, Faraone, Biederman, Poldrack, & Seidman, 2005). The classic n-back task usually consists of the sequential presentation of letters on the screen, and the participant is instructed to respond if the presented letter and the letter shown 'n' trials earlier are identical (J. D. Cohen et al., 1994). In contrast, a frequently used modification of this task uses numbers instead of letters and requires the participant to respond on every trial by indicating the number (numbers 1 to 4) shown 'n' trials earlier (Goldberg et al., 2003). We decided to use this modified version of the n-back task, as it was previously successfully employed to assess the effects of *COMT* genotype on functional activation in the frontal lobes, yielding significant differences between the three allele groups (Diaz-Asper et al., 2008; Egan et al., 2001). Moreover, this task was shown to be sensitive to interactions of *COMT* genotype and amphetamine intake in healthy controls (Mattay et al., 2003).

The goal of this study was to compare behavioural performance and functional activation of aADHD patients and healthy controls as well as to investigate the effect of stimulant medication on several neuropsychological tests, the previously established selective attention task, and the modified n-back task. In addition, this study tried to explore possible interactive effects of *COMT* genotype and aADHD. Throughout the investigation of task-induced functional activation, a particular focus was placed on the attention/ task-positive network.

5.2 Methods

5.2.1 ADHD Patient Sample and Healthy Control Sample

A total of 41 adult patients with ADHD were recruited from the ADHD outpatient clinic at the Department of Psychiatry, Psychosomatics, and Psychotherapy of the University of Würzburg. Diagnoses were made by an experienced psychiatrist according to DSM-IV-TR (2000) criteria. Patients had to be medication naïve or without medication for at least three months prior to

testing. Three of the recruited aADHD patients did not meet full inclusion criteria[7]. Three more patients decided not to proceed with the study after inclusion and one patient decided to discontinue the study after the first fMRI appointment for unknown reasons. No or only one set of fMRI data was obtained from two patients who worked in metal processing and were excluded from further fMRI data collection in accordance with MRB safety requirements. This resulted in a total of 35 data sets from patients with ADHD, of whom 34 participated in the first fMRI appointment and 32 participated in the first as well as in the second fMRI appointment. Of the 35 patients who participated in the study, 19 patients (54 %) were classified as predominantly inattentive (based on CAARS DSM-IV T-scores > 60 on the Inattentive Symptoms scale), 15 patients (43 %) were classified as combined type (based on CAARS DSM-IV T-scores > 60 on the Inattentive as well as on the Hyperactive/ Impulsive Symptoms scale), and one patient was classified as predominantly hyperactive/ impulsive (based on CAARS DSM-IV T-scores > 60 on the Hyperactive/ Impulsive Symptoms scale). The patient classified as suffering from ADHD of the predominantly hyperactive/ impulsive type discontinued the study after the first fMRI appointment.

After inclusion in the study, all patients were randomly assigned to either IR-MPH or placebo treatment in a double-blind design. Neither the patients nor any researcher involved in data collection were aware of the assigned treatment. Medication was dispensed in a free titration design. The medication schedule started with a daily dose of 10 mg, which was increased by 10mg every week up to a maximum daily dose of 60 mg. Medication was only increased as long as the patient subjectively benefitted from the increase without suffering from any disturbing side effects. A psychiatrist saw each participating patient at least every two weeks to assess symptom response and side effects, and adjust medication dosage if necessary. Patients were debriefed after the second fMRI appointment following six weeks of MPH medication or placebo and could subsequently begin or continue with MPH medication (depending on their previous treatment), if they wished. Furthermore, all patients were seen by a psychiatrist for a final follow-up

[7] See Table 8.2 and below (appendix) for the full list of inclusion and exclusion criteria, and for characteristics of the dispensed MPH and placebo medication.

assessment four weeks after the end of the double-blind medication phase (see Figure 5.1).

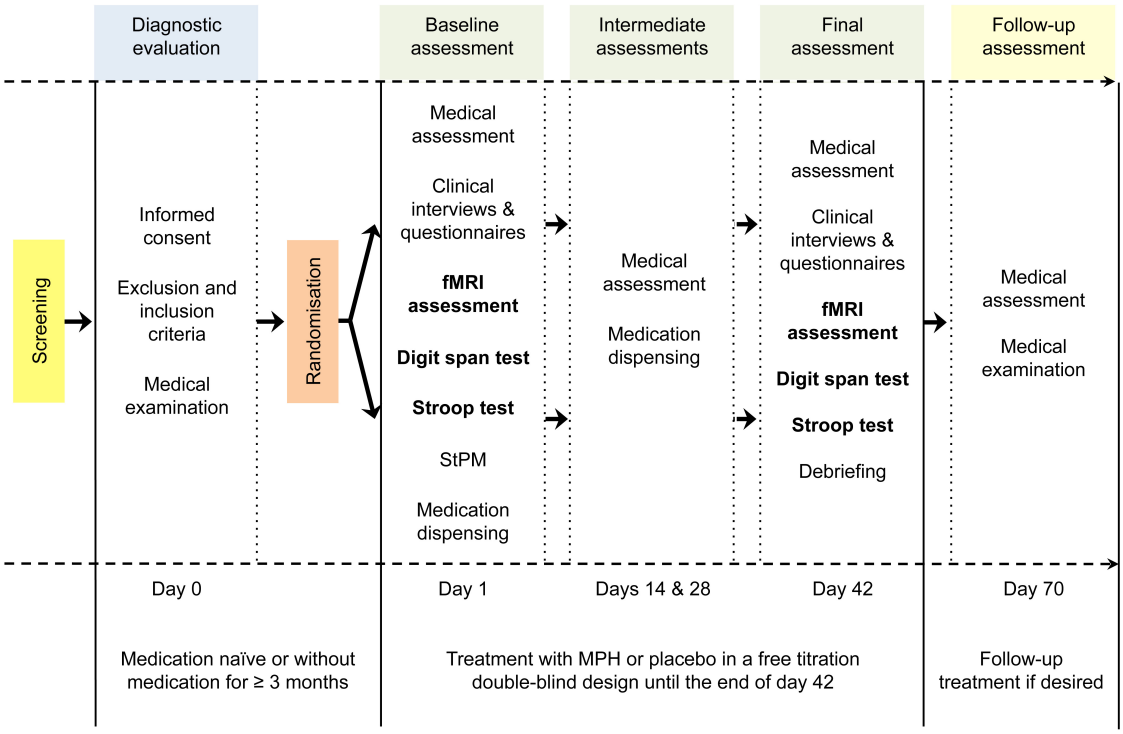

Figure 5.1: Schematic diagram illustrating the time profile of the clinical trial. For a detailed description of the employed clinical and neuropsychological measures see 5.2.2.

In addition, 47 healthy control participants without a past or present diagnosis of ADHD were recruited from a previously established participant pool (see also Biehl et al., 2013; Gschwendtner et al., 2012) as well as through university advertisement. A varying subset of healthy control participants was chosen as a most closely matched control group for the experimental tasks following a case-control design ($p > .2$ for age, gender, and number of school years). All control participants had normal or corrected-to-normal vision and were free of neurological or psychiatric diseases.

Furthermore, all participants were genotyped for the *COMT* val^{158}met polymorphism. Blood was taken and DNA was extracted using a standard de-salting procedure. A standard PCR procedure (slightly modified from the protocol used by Egan et al., 2001) was used to determine *COMT* genotypes, which did not

deviate from Hardy-Weinberg equilibrium. Ethical approval was obtained through the Ethical Review Board of the medical faculty of the University of Würzburg; all procedures involved were in accordance with the 2008 Declaration of Helsinki. All participants gave written informed consent after full explanation of the procedures.

5.2.2 Psychological Assessment

Patients were administered the Wender-Reimherr-Interview (WRI), a semi-structured interview to aid the diagnosis of aADHD (Corbisiero, Buchli-Kammermann, & Stieglitz, 2010). In addition, patients completed the CAARS (Conners et al., 1999), which is a more refined questionnaire of aADHD (Christiansen et al., 2012; Christiansen et al., 2011) and the WURS (Ward et al., 1993), which assesses childhood symptoms of ADHD. To exclude possible comorbid axis I disorders, all patients were assessed with the Structured Clinical Interview for DSM-IV (SCID-I) (Wittchen, Zaudig, & Fydrich, 1997), the Hamilton Depression Rating Scale (HAM-D) (Hamilton, 1960), and the Hamilton Anxiety Rating Scale (HAM-A) (Hamilton, 1959). With exception of the WURS, all of the questionnaires were administered before the first and the second fMRI appointment in order to track possible treatment-related changes in symptomatology.

Patients as well as healthy controls completed the ASRS (R. C. Kessler et al., 2005), an 18-item screening questionnaire assessing ADHD symptoms based on the DSM-IV-TR (2000), and the PANAS (Krohne et al., 1996; Watson et al., 1988) to control for positive and negative affectivity at the time of the fMRI appointments. In addition, the following neuropsychological data were obtained from all participants during the first (and for patients also during the second) fMRI appointment: The *Digit Span* subtest from the German version of the WAIS (Aster, Neubauer, & Horn, 2006) as a measure of verbal short-term memory (*Digit Span Forward*) and verbal working memory (*Digit Span Backward*), the Stroop *Color Word Test* (Bäumler, 1985) as a measure of inhibition, and the Standard

Progressive Matrices (StPM)[8] (Kratzmeier & Horn, 1988) to obtain an estimate of intellectual functioning. The StPM was administered only once since it assesses fluid intelligence, which should not vary as a result of stimulant medication treatment.

5.2.3 fMRI Data Acquisition and Analysis

As for the pilot study, imaging data were acquired at the MRB using a Siemens MAGNETOM® Avanto MRI scanner with a magnetic field strength of 1.5 Tesla (Siemens AG, Erlangen, Germany) and a twelve channel head coil. The presentation and response equipment were identical to the equipment described in 4.3.4. For all paradigms, TR of the T2*-weighted gradient EPI sequence was three seconds; the echo time (TE) was 50 milliseconds. Further parameters were flip angle (90°), in-plane resolution 3.6 × 3.6 mm^2, field of view (FOV) 230 × 230 mm^2. One TR allowed for the serial acquisition of 32 axial slices of 4 mm thickness in descending order (1 mm gap between slices). Slices were aligned to be parallel to the AC-PC line, which runs along the anterior and the posterior commissure. The first three volumes of each sequence were discarded to allow for signal saturation. In addition, a high-resolution structural MPRAGE scan was acquired for every participant as described above.

All fMRI data were analysed using SPM8 (Wellcome Trust, 2009) as described in 4.3.4. As described in 5.2, a separate subgroup of healthy participants was chosen for each task to match the ADHD patients most closely. To examine task-induced activation, whole brain analyses were carried out across both groups by performing one-sample t-tests with $p_{FWE} < .05$ for the contrasts of interest. These results were subsequently examined for activation at peak voxels of interest belonging to the task-positive network as specified by Fox and colleagues (2006; 2005). To reduce the number of tests, further analyses were only conducted if the examined contrast caused significant activation of the peak voxel across all

[8] The abbreviation *StPM* was chosen to avoid confusion with the fMRI analysis software Statistical Parametric Mapping (SPM).

participants. To investigate differences between the aADHD and the control group, whole brain analyses were carried out by performing two-sample t-tests with $p_{FWE} < .05$ for the contrasts of interest. Medication effects were examined using mixed model ANOVAs implemented as flexible factorial models in SPM8 with the between-subjects factor *medication* (MPH versus placebo) and the within-subjects factor *time of measurement* (first fMRI appointment versus second fMRI appointment).

Further analyses were carried out by testing for differences between aADHD patients and healthy controls as well as between MPH- and placebo-treated aADHD patients using small volume correction (spheres with 9 mm radius placed around the MNI transformed coordinates of the peak voxels from Fox et al., 2005, 2006). For all analyses, peak voxels with $p_{FWE} \leq .05$ were considered significant and peak voxels with $p_{FWE} \leq .1$ were considered trends. If the small volume correction showed a significant between-group difference or trend for the peak voxel of a given cluster, the contrast estimates of this cluster were exported for each participant using REX Toolbox (Whitfield-Gabrieli, 2009). These mean cluster activations were then entered into SPSS Statistics 20 (IBM®, New York, USA) for further analysis and correlations between cluster activations and behavioural as well as questionnaire data were computed[9]. For illustration purposes, the fMRI data below are rendered using MRIcron (Rorden, 2010) by overlaying the clusters on a template with 16 mm search depth.

For the selective attention task, individual FFA activation was extracted for high distracting task irrelevant face stimuli minus face stimuli from the passive viewing control condition as well as for task relevant face stimuli minus face stimuli from the passive viewing control condition using REX Toolbox (Whitfield-Gabrieli, 2009) as described in 4.3.4. FFA ROIs were created for each participant by examining individual first-level results of the contrast 'faces minus swirled faces' from the functional localiser (see 4.3.1 and 5.5.2 for a description of this localiser).

[9] As in the previous fMRI study, mean cluster activation was used for further analyses as a more robust measure of regional activation. Correlations and *COMT* genotype analyses using peak voxel activation instead of cluster activation yielded similar results and are reported in the appendix (see Table 8.4 and 8.3.3).

5.2.4 Statistical Analysis

Potential differences in behavioural performance and/or the exported mean cluster activations between the aADHD group and the healthy control group were investigated using two-sample t-tests with the between-subjects factor *group* (aADHD versus healthy controls) for the selective attention task. For the n-back task, mixed model ANOVAs with the between-subjects factor *group* (aADHD versus healthy controls) and the within-subjects factor *task difficulty* (0-back, 1-back, 2-back) were computed. To investigate medication effects on behavioural performance and/or mean cluster activation, mixed model ANOVAs with the between-subjects factor *medication* (MPH versus placebo) and the within-subjects factor *time of measurement* (first fMRI appointment versus second fMRI appointment) were computed for the selective attention task. For the n-back task, mixed model ANOVAs with the between-subjects factor *medication* (MPH versus placebo) and the within-subjects factors *time of measurement* (first fMRI appointment versus second fMRI appointment) and *task difficulty* (0-back, 1-back, 2-back) were computed.

Furthermore, FFA activation in the selective attention task was analysed using a mixed model ANOVA with the between-subjects factor *group* (ADHD patients versus healthy controls) and the within-subjects factor *task relevance* (high distracting task irrelevant versus task relevant). Hypotheses-driven one-sided t-tests were used for the factor *task relevance* in the selective attention task; two-tailed t-tests were used for all other post-hoc comparisons. To control for multiple comparisons, all post-hoc t-tests were Šidák-corrected. If assumptions of sphericity were violated, degrees of freedom were adjusted according to Greenhouse-Geisser (Greenhouse & Geisser, 1959). However, to facilitate understanding only full degrees of freedom are reported. In addition, correlations between cluster activations and performance data as well as CAARS scores (for the patient group) were computed.

For all behavioural data, outliers were identified using *z*-transformation of the data. Participants with any value exceeding $z = \pm 3.29$ were excluded from further data analysis. For the selective attention task, an additional accuracy index

incorporating both the number of correctly identified targets and the number of false alarms was calculated as described above.

The interaction of *COMT* genotype and ADHD diagnosis was investigated whenever the number of participants allowed meaningful exploratory analyses. Unfortunately, this was not the case for the selective attention task (n = 4 in the smallest cell). Unlike originally intended, the interaction of *COMT* genotype and medication response in the ADHD sample could also not be investigated, with the smallest cells ranging from n = 1 to n = 3 for the different tasks. Given the unequal and partially rather small cell sizes caused by the distribution of the *COMT* genotype in the general population, all *COMT* genotype data were analysed using a non-parametric equivalent of the two-way ANOVA which ranks observations for the levels of one factor within the levels of the other factor (Prescott & Shahlaee, 1999; Shirley, 1987), with ADHD diagnosis and *COMT* genotype entered as fixed factors in all analyses. Mann-Whitney-U tests for independent samples were used for post-hoc comparisons. For all analyses, *p*-values of $\alpha \leq .05$ were considered significant and *p*-values of $\alpha \leq .1$ were considered trends.

5.3 Clinical Outcomes

As mentioned above, patients were randomly assigned to either MPH or placebo treatment in a double-blind design. Medication was dispensed in a free titration design meaning that dosage was only increased as long as the patient reported beneficial effects without suffering from any disturbing side effects. After six weeks of medication, the average daily medication dose was 49 mg (*SD* = 15). Medication doses were significantly lower for patients in the MPH (*M* = 44 mg, *SD* = 18) compared to patients in the placebo group (*M* = 55 mg, *SD* = 8; $t_{(32)} = 2.48$, $p = .02$).

In line with previous studies (Biederman, Mick, et al., 2010; Medori et al., 2008; Rösler et al., 2009), clinically significant treatment response was defined as a fixed minimum reduction in T-scores, in this case on the CAARS DSM-IV Total ADHD Symptoms scale as well as on the CAARS DSM-IV Inattentive Symptoms

scale and/or the CAARS DSM-IV Hyperactive/ Impulsive Symptoms scale, from day 1 to day 42. Given that the CAARS scores in this study were based on self-report, we deemed a minimum reduction of 20 % sufficient to classify patients as responders. Across both the MPH and the placebo group, 18 patients (53 %) were classified as responders. Six patients (40 %) in the placebo group and 12 patients (63 %) in the MPH group responded to treatment, yielding a trend for a significant between-group difference ($t_{(32)} = 1.34$, $p_{\text{one-sided}} = .095$).

These results were similar when absolute CAARS DSM-IV T-scores instead of response rates based on symptom reduction were compared, although mixed model ANOVAs with the between-subjects factor *medication* and the within-subjects factor *time of measurement* showed no significant interaction of these factors for any of the ASRS or the CAARS DSM-IV subscales (all $p > .1$). There was, however, a significant main effect of time of measurement on both ASRS and all three CAARS DSM-IV subscales (ASRS inattention: $F_{(1,32)} = 14.91$, $p = .001$; ASRS hyperactivity/ impulsivity: $F_{(1,32)} = 16.34$, $p < .001$; CAARS DSM-IV Inattentive Symptoms: $F_{(1,32)} = 29.90$, $p < .001$; CAARS DSM-IV Hyperactive/ Impulsive Symptoms: $F_{(1,32)} = 17.14$, $p < .001$; CAARS DSM-IV Total ADHD Symptoms: $F_{(1,32)} = 32.49$, $p < .001$; see Table 5.1) with both groups reporting more symptoms before the first fMRI appointment than after six weeks of MPH medication or placebo. In addition, there was a significant main effect of medication on the ASRS inattention score ($F_{(1,32)} = 5.09$, $p = .03$) and a trend for a main effect of medication on the ASRS hyperactivity/ impulsivity score ($F_{(1,32)} = 3.78$, $p = .06$) and on the CAARS DSM-IV Hyperactive/ Impulsive Symptoms score ($F_{(1,32)} = 3.50$, $p = .07$), with the placebo group's score across both appointments being higher than the MPH group's.

This pattern of results became even clearer when the individual percentage of score reduction for each patient was compared for the two groups using hypothesis-driven one-sided independent sample t-tests. As suggested by the two previous analyses, the MPH group showed a trend for a more pronounced decrease in CAARS DSM-IV Inattentive Symptoms scores than the placebo group ($t_{(32)} = 1.38$, $p = .09$). Findings were similar albeit less pronounced for CAARS DSM-IV Total ADHD Symptoms scores ($t_{(32)} = 1.15$, $p = .13$), whereas no probable differences in

symptom reduction between the two groups could be surmised for the CAARS DSM-IV Hyperactive/ Impulsive Symptoms scores ($t_{(32)} = 0.39$, $p = .35$).

Potential explanations for these findings are discussed in 6.2 below.

Table 5.1: Overview of mean ASRS and mean CAARS DSM-IV scores as well as mean percentage CAARS T-score reduction for the ADHD group. Standard deviation is noted in parentheses unless stated otherwise.

	1st/2nd appointment (ADHD)	
	Placebo	MPH
Participants (male)	15 (9)	19 (10)
ASRS (raw-scores)		
Inattention	25.0(*4.5*)/21.2(*8.5*)	23.6(*5.4*)/15.3(*7.0*)
Hyperactivity/Impulsivity	20.1(*5.7*)/16.5(*7.4*)	18.2(*7.5*)/11.1(*5.9*)
CAARS (T-scores)		
Inattentive Symptoms	79.1(*8.9*)/67.1(*14.7*)	80.1(*9.6*)/61.2(*13.3*)
Reduction (percentage)	13.8(*21.7*)	23.0(*17.1*)
Hyperactive/Impulsive Symptoms	65.9(*15.0*)/54.9(*13.6*)	58.2(*14.9*)/46.6(*15.0*)
Reduction (percentage)	14.5(*19.8*)	17.5(*24.6*)
Total ADHD Symptoms	76.7(*11.7*)/62.9(*14.9*)	73.0(*11.7*)/54.9(*14.6*)
Reduction (percentage)	16.3(*21.4*)	24.1(*18.0*)

Note. Both groups reported significantly more symptoms before the first fMRI appointment than after six weeks of MPH medication or placebo (all $p < .001$).

5.4 Neuropsychology and Questionnaires[10]

As detailed in 1.1.3 (3), studies with children and adolescents with ADHD report a beneficial effect of MPH on working memory measures requiring a manipulation of maintained material as well as on working memory measures

[10] Results from the following study are currently submitted for publication.

requiring simple information storage and reproduction (Coghill et al., 2013). In addition, one study investigating adults with ADHD found a significant improvement of test scores on the Stroop as well as on a working memory index comprising arithmetic and digit span subtests (Fallu et al., 2006).

Furthermore, several studies investigated the impact of *COMT* genotype on neuropsychological endophenotypes in ADHD (see also 1.2.3). So far, four studies investigating children and adolescents provided some evidence that val/val carriers might perform worse on tasks taxing short-term information storage while met-allele carriers might be impaired on measures of sustained attention (Bellgrove et al., 2005; Matthews et al., 2012; Mills et al., 2004; Taerk et al., 2004). Crucially, it should be noted that the importance of COMT increases with increasing age (Barnett et al., 2008; Levy, 2007), meaning its functional impact on PFC mediated higher cognitive functions should be more visible in adults than it is in children (Taerk et al., 2004). However, there is only one study with aADHD patients to date (Boonstra et al., 2008). While this study found a positive association for the val/met genotype and full-scale IQ on the WAIS, there was no effect of *COMT* genotype on the subtests *Digit Span Forward* or *Digit Span Backward* or on the Stroop *Color Word Test*. Unfortunately, none of these studies used a healthy control group, thereby potentially missing differential effects of *COMT* in ADHD patients compared to healthy controls.

The aim of this study was therefore to investigate the neuropsychological performance of aADHD patients compared the healthy controls. In a second step, a possible interactive impact of *COMT* genotype and ADHD diagnosis as well as possible effects of stimulant treatment on neuropsychological task performance in aADHD patients was examined.

5.4.1 Hypotheses

1. In line with previous studies (Boonstra et al., 2005; Martinussen et al., 2005; Willcutt et al., 2005), aADHD patients should perform worse on the investigated neuropsychological EF measures of verbal short-term memory (*Digit Span Forward*), verbal working memory (*Digit Span Backward*), and inhibition (Stroop *Color Word Test*) than healthy controls.
2. Regarding a possible medication effect in the aADHD group, we expected a positive impact of MPH on the examined measures, with the MPH group performing better than the placebo group after six weeks of treatment (Coghill et al., 2013; Fallu et al., 2006).
3. Based on the tonic-phasic model of dopaminergic functioning (Arnsten, 2006; Bilder et al., 2004; Grace, 1991; Pliszka, 2005), the *COMT* val-allele should furthermore be more detrimental to aADHD patients than to healthy controls in a gene-dosage fashion, with val/val aADHD patients showing the worst performance.

5.4.2 Participants

Neuropsychological and questionnaire data were obtained from 35 adult patients with ADHD and 35 healthy controls comparable with regard to age, gender, and school years (all $p>.2$, with the exception of school years $p = .15$; see Table 5.2 for sample characteristics).

Table 5.2: Overview of mean demographic data, ASRS and StPM scores, and distribution of COMT genotype for the neuropsychological tasks for healthy controls (HC) and patients with ADHD. Standard deviation is noted in parentheses unless stated otherwise.

	1st appointment		1st/2nd appointment (ADHD)	
	HC	ADHD	Placebo	MPH
Neuropsychology				
Participants (male)	35 (16)	35 (20)	15 (9)	19 (10)
Mean age	33.6(*9.6*)	36.0(*9.9*)	35.3(*10.2*)	37.2(*9.7*)
Mean school years	11.2(*1.8*)	10.6(*1.6*)	10.4(*1.4*)	10.8(*1.8)*
StPM raw score	49.0(*7.8*)	49.1(*6.9*)	49.6(*7.7*)	48.8(*6.5*)
Mean inattention[1]	11.5(*4.7*)*	23.9(*5.2*)*	25.0(*4.5*)/21.2(*8.5*)	23.6(*5.4*)/15.3(*7.0*)
Mean hyperactivity	9.7(*5.8*)*	19.1(*6.6*)*	20.1(*5.7*)/16.5(*7.4*)	18.2(*7.5*)/11.1(*5.9*)
COMT genotype				
met/met (male)	8 (3)	10 (8)		
val/met (male)	17 (9)	18 (8)		
val/val (male)	10 (4)	7 (4)		

Note. [1] Symptoms of inattention and hyperactivity/ impulsivity as assessed with the ASRS; * denotes significant between-group differences ($p < .001$).

5.4.3 Results

5.4.3.1 Patients with ADHD versus Healthy Controls

As would be expected, patients with ADHD had significantly more symptoms of inattention and hyperactivity/ impulsivity compared to healthy controls as assessed with the ASRS before the first fMRI appointment (inattention: $t_{(68)} = 10.48$, $p < .001$; hyperactivity/ impulsivity: $t_{(68)} = 6.25$, $p < .001$; see Table 5.2). There were no significant between-group differences on the StPM or on any of the other neuropsychological measures (all $p > .1$).

5.4.3.2 ADHD Patients with MPH Medication versus Placebo

Mixed model ANOVAs with the between-subjects factor *medication* and the within-subjects factor *time of measurement* yielded no significant main effects or interactions for the *Digit Span Forward* and *Digit Span Backward* subtests (all $p > .1$). For the Stroop *Color Word Test*, results showed no significant interaction of medication and time of measurement, but a significant main effect of time of measurement ($F_{(1,32)} = 28.45$, $p < .001$) with all participants performing significantly better on the second ($M = 67.8$ s, $SD = 14.5$) than on the first appointment ($M = 74.8$ s, $SD = 16.4$).

5.4.3.1 Interaction of *COMT* Genotype and ADHD Diagnosis

For the *Digit Span Forward* subtest (verbal short-term memory), there was no significant main effect of ADHD diagnosis ($p = .16$) or *COMT* genotype ($p = .28$). There was, however, a trend for an interaction of ADHD diagnosis and *COMT* genotype ($F_{(2,64)} = 2.81$, $p = .07$). Post-hoc Mann-Whitney-U tests revealed a significant difference between the two groups for the met/met genotype ($p = .03$), with the ADHD group performing significantly worse than the healthy control group (see Figure 5.2). Within the patient group, val/met carriers performed significantly better than met/met carriers ($p = .01$), while there were no significant differences within the healthy control group.

For the *Digit Span Backward* subtest (verbal working memory), there similarly was no significant main effect of ADHD diagnosis ($p = .24$) or *COMT* genotype ($p = .85$). However, there was a significant interaction of ADHD diagnosis and *COMT* genotype ($F_{(2,64)} = 3.27$, $p = .04$). Post-hoc Mann-Whitney-U tests revealed a significant difference between the two groups for the val/val genotype ($p = .03$) with the group with ADHD performing significantly worse than the healthy control group (see Figure 5.2). In addition, val/val carriers performed significantly better than val/met carriers ($p = .02$) within the healthy control group. There were no significant differences within the patient group.

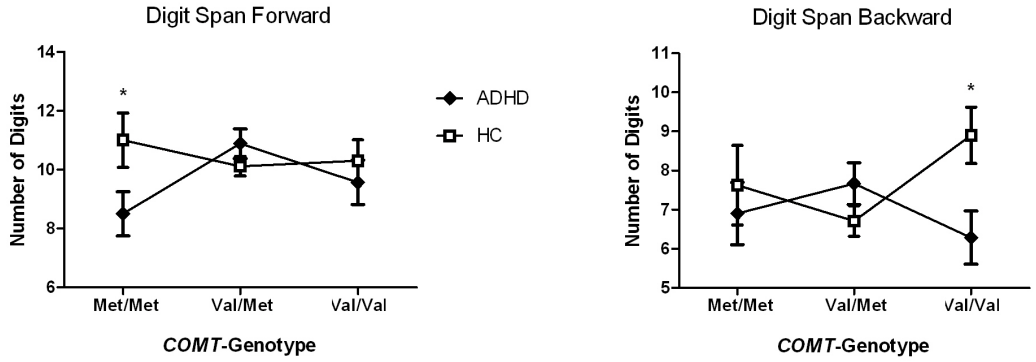

Figure 5.2: Mean number of repeated digits in the *Digit Span Forward* and in the *Digit Span Backward* subtest for patients with ADHD and healthy controls (HC) and the different *COMT* genotypes. Error bars denote standard error of the mean (SEM). Significant between-group differences ($p < .05$) are marked by *.

For the Stroop *Color Word Test* (inhibition), there was no significant main effect of ADHD diagnosis or *COMT* genotype as well as no significant interaction of the two (all $p > .1$).

5.4.4 Discussion

Contrary to our hypotheses, healthy controls did not perform significantly better than aADHD patients on the examined neuropsychological measures of verbal working memory, verbal short-term memory, and inhibition. Investigation of the medication effects in aADHD patients also did not yield the hypothesised results. Patients in the MPH group did not show an improved performance after six weeks of treatment on any of the examined neuropsychological measures when compared to the placebo group.

In contrast, measures of verbal short-term memory and verbal working memory showed interaction effects of *COMT* genotype and ADHD diagnosis. Interestingly, the results showed a differential effect of *COMT* genotype and ADHD depending on the nature of the task: While met/met carriers with ADHD seemed to be at a disadvantage on the measure of verbal short-term memory compared to the

other genotypes and healthy controls, the measure of verbal working memory did not seem to benefit val/val carriers with ADHD in the same way as healthy val/val carriers. These results can be interpreted in terms of the tonic-phasic model of increased stability or flexibility depending on *COMT* genotype (Barnett et al., 2008; Bilder et al., 2004; Durstewitz & Seamans, 2008; Matthews et al., 2012): The measure of verbal short-term memory (*Digit Span Forward*) required the reproduction on increasingly long lists of numbers. It would therefore seem reasonable for met/met carriers to show better performance as increased tonic dopamine – and thereby increased representational stability – would be advantageous in this task. However, compared to the healthy control group, met/met carriers with ADHD showed worse performance. This finding is in line with another study that reports worse performance for met-allele carriers with ADHD on a measure of sustained (i.e. stable) attention (Bellgrove et al., 2005). In contrast, the measure of verbal working memory (*Digit Span Backward*) required the retention of lists of numbers as well as the internal manipulation of these lists before reproduction. It could therefore be expected that val/val carriers show better performance as this genotype affords increased phasic dopamine and thereby increased mental flexibility. Again, patients with ADHD did not show this expected advantage compared to healthy controls.

As overall sample size for the analysis of a medication effect was rather small, interaction effect sizes (Cohen's *f*) were calculated for the non-significant results based on partial η^2 and corrected for correlation among repeated measures using G*Power 3.0.3 (Faul, Erdfelder, Lang, & Buchner, 2007) to explore whether sample size was sufficient to detect significant interactions of the factors *time of measurement* and *medication*. Unlike effect sizes for the better known Cohen's *d*, effect sizes for Cohen's *f* are considered as small if they exceed .1, medium if they exceed .25, and large if they exceed .4 (J. Cohen, 1988; UCRegents, 2013). Interaction effect size for the *Digit Span Forward* subtest was below .001 and hence no power calculation was performed. Achieved power was high for the Stroop *Color Word Test* (Cohen's $f = .13$, power = .89) as the two Stroop measurements correlated substantially, and it should therefore be assumed that sample size was sufficient for statistical analysis to detect any truly existing interaction effect.

Power was considerably lower, however, for the *Digit Span Backward* subtest (f = .11, power = .27) allowing for the possibility that a potential interaction effect was missed due to insufficient sample size. Still, it should be noted that the interaction effect sizes for both neuropsychological tests were relatively small pointing to only a minor effect of medication on test performance.

In addition, although the data yielded no main effects of *COMT* genotype or ADHD on the investigated neuropsychological measures, two of the three tasks showed interactions of *COMT* genotype and ADHD diagnosis. The results therefore point to a possible differential impact of *COMT* genotype in adults with ADHD compared to healthy controls. However, given the relatively small overall sample size, these results should be interpreted with caution and more research is clearly necessary.

5.5 Selective Attention Task

As the experimental paradigm of this task was successfully transferred from EEG to fMRI in the previous study (see 4.5), the goal of this study was to assess behavioural performance and functional brain activity in aADHD patients and healthy controls, and to examine possible effects of MPH medication on these parameters in aADHD patients. As stated above, the first (EEG) study provided some indication of subclinical ADHD symptoms impacting on processing modulation as well as on target detection rates and performance accuracy. Based on previous studies which successfully transferred investigations from participants with subclinical ADHD symptoms to ADHD patient samples (e.g. Herrmann et al., 2010; Herrmann et al., 2009), we expected the performance profiles of aADHD patients to be similar to those of the participants with subclinical ADHD symptoms, but potentially more strongly impaired. Our second (fMRI) study furthermore showed activation of participants' task-positive network including the left MFG/DLPFC when high distracting task irrelevant and task relevant stimuli were compared. Since previous studies report a hypoactivation of the DLPFC and the frontoparietal/ task-positive network in ADHD (Banich et al.,

2009; Cortese et al., 2012; Valera et al., 2010) as well as a possible up-regulation of frontoparietal/ task-positive network activation through MPH (Cubillo et al., 2013; Wong & Stevens, 2012), a particular focus of this study was on the activation of these networks as well as potential medication-induced changes in network activation.

5.5.1 Hypotheses

1. Based on the previous fMRI results for this paradigm, we hypothesised that high distracting task irrelevant stimuli would lead to increased activation of frontal nodes of the attention/ task-positive network compared to task relevant stimuli (Gazzaley et al., 2005; Jha et al., 2004).
2. This activation should be lower in aADHD patients compared to healthy controls (Cortese et al., 2012), and it should correlate negatively with symptoms of hyperactivity/ impulsivity and inattention in the patient sample.
3. At the end of the clinical trial, patients who received MPH treatment should show increased network activation both compared to their first measurement and compared to patients who received placebo treatment (Cubillo et al., 2013; Wong & Stevens, 2012).
4. With regard to individually determined FFA activation, we again expected high distracting task irrelevant stimuli to lead to increased activation compared to task relevant stimuli (Jha et al., 2004), and we expected frontal activation for high distracting task irrelevant stimuli minus to task relevant stimuli to correlate positively with FFA activation for the same contrast (Gazzaley et al., 2007).
5. In addition, we hypothesised that differential FFA activation for high distracting task irrelevant stimuli minus task relevant stimuli would correlate negatively with ADHD symptoms as reported on the CAARS.

6. Given the results obtained in the first (EEG) study, we furthermore expected the percentage of detected targets and the accuracy index to correlate negatively with CAARS DSM-IV Hyperactive/ Impulsive Symptoms as well as CAARS DSM-IV Total ADHD Symptoms scores.

5.5.2 Experimental Paradigm

The experimental paradigm was a modification of the selective attention tasks used in the first (EEG) and in the second (fMRI) study (see 3.3.1 and 4.3.1). Following the results of the second study, task relevant house stimuli were omitted from the paradigm and the occurrence probability of passively viewed house stimuli was reduced. The modified experimental paradigm therefore comprised only two conditions: One experimental condition ("faces relevant") and a passive viewing control condition. Each condition was presented twice, yielding a total of four blocks containing 80 stimuli each. Of the 80 stimuli presented in the experimental condition, 40 (i.e. 50 % of all stimuli presented in the block) were task relevant and 40 (i.e. another 50 %) were task irrelevant distractors. The 40 task relevant stimuli were all face stimuli. In contrast, the 40 task irrelevant stimuli were split evenly to be either face stimuli (yielding 20 high distracting task irrelevant stimuli) or house stimuli (yielding 20 low distracting task irrelevant stimuli). The passive viewing control condition contained 30 face stimuli (i.e. 75 % of all presented stimuli) and 10 house stimuli (i.e. 25 %), which – only in this condition – were presented in random order. Every picture was shown only once in one of the two conditions.

The occurrence probability of 1-back and 2-back repetitions remained unchanged from the original task. However, interstimulus intervals were further increased to improve the detection of potential effects, and now lasted 3,000 ms to 6,000 ms. On a behavioural level, reaction times for correct responses as well as number of false alarms and number of correctly identified target stimuli were recorded. In addition, the functional localiser was modified to include only face pictures. Half of these face pictures were made unrecognisable by using a 600

degree swirl filter as implemented in Adobe® Photoshop® CS4 (version 11.0, Adobe Systems, Inc., San Jose, USA). As some participants had shown difficulties in task understanding in the previous fMRI study, all participants now completed a computerised explanation of all tasks with subsequent supervised practice sessions to ensure a good understanding of task requirements.

5.5.3 Participants

At the first fMRI appointment, fMRI data of 33 patients with ADHD were obtained. Two data sets were lost because of technical problems. Two patients had to be excluded after preprocessing of the data because of excessive movement in the scanner (continuous repetitive movements and sudden movement of more than 2 mm, respectively). Three patients were excluded because their behavioural data showed extreme outlier values for false alarms, and another two patients were excluded because they detected less than 40 % of the target trials and their understanding of the experimental task was therefore doubtful. This resulted in a total of 24 patient data sets for this task at the first appointment. The control group was chosen from the total sample of healthy participants to be comparable (all $p \geq .2$) to the aADHD group with regard to age, gender, and years of schooling (see Table 5.3 for sample characteristics).

Three more patient data sets were lost at the second fMRI appointment: One patient discontinued the study after the first fMRI appointment for unknown reasons, while a second patient could not participate in the second fMRI appointment due to MRB safety requirements (work in metal processing), and a third patient showed poor target detection (< 40 %) at the second fMRI appointment. This resulted in a total of 21 patient data sets that comprised both the first fMRI appointment without medication and the second fMRI appointment after 6 weeks of MPH or placebo treatment (see Table 5.3).

Table 5.3: Overview of mean demographic data and ASRS scores for healthy controls and patients with ADHD as well as ADHD placebo and MPH groups for the selective attention task. Standard deviation is noted in parentheses unless stated otherwise.

	1st appointment		1st/2nd appointment (ADHD)	
	Controls	ADHD	Placebo	MPH
Selective attention				
Participants (male)	24 (12)	24 (13)	11 (6)	10 (4)
Mean age	34.4(*9.0*)	37.4(*8.9*)	38.5(*9.2*)	39.2(*8.4*)
Mean school years	10.9(*1.8*)	10.7(*1.5*)	10.5(*1.3*)	11.0(*1.8*)
StPM raw score	49.8(*5.8*)	50.3(*6.6*)	49.4(*7.7*)	50.6(*5.7*)
Mean inattention[1]	11.3(*4.9*)*	24.0(*5.1*)*	25.4(*4.4*)/21.7(*7.9*)	23.2(*5.5*)/15.2(*6.5*)
Mean hyperactivity	9.5(*5.9*)*	19.3(*6.1*)*	19.5(*5.2*)/15.5(*5.7*)	17.7(*6.9*)/11.6(*6.3*)

Note. [1] Symptoms of inattention and hyperactivity/ impulsivity as assessed with the ASRS; * denotes significant between-group differences ($p < .001$).

5.5.4 Results

5.5.4.1 Patients with ADHD versus Healthy Controls

(1) Behavioural Data

Two-sample t-tests with the between-subjects factor *group* for the percentage of correctly identified target stimuli (hits), the number of false alarms, reaction time, and overall accuracy showed no behavioural differences between the two groups (all $p > .1$). Both groups had an overall accuracy index of around .95 and detected around 80 % of the target trials with an average reaction time of around 960 ms and committed around 5 false alarms (see Table 5.4 for the performance parameters of the different groups).

Table 5.4: Overview of mean performance parameters for healthy controls and patients with ADHD as well as ADHD placebo and MPH groups in the selective attention task. The standard deviation is noted in parentheses.

	1st appointment		1st/2nd appointment (ADHD)	
	Controls	ADHD	Placebo	MPH
Selective attention				
% hits	80.8(*19.1*)	82.5(*16.7*)	83.6(*15.7*)/ 85.5(*15.1*)	84.0(*19.6*)/ 78.0(*11.4*)
Reaction time[1]	951(*278*)	969(*363*)	895(*261*)/ 998(*440*)	1047(*408*)/ 1184(*481*)
False alarms	6.3(*6.2*)	4.9(*5.6*)	4.4(*4.8*)/3.5(*3.6*)	3.9(*3.6*)/1.5(*1.4*)
Accuracy index	.95(*.04*)	.96(*.04*)	.96(*.04*)/.97(*.03*)	.97(*.03*)/.98(*.01*)

Note. [1] Reaction time is reported in milliseconds (ms). There were no significant between-group differences (all $p > .1$).

(2) fMRI Data

As in the previous fMRI study, the contrast of high distracting task irrelevant stimuli minus task relevant stimuli was examined to investigate selective attention processes. Across all participants, the whole brain analysis with $p_{FWE} < .05$ for this contrast showed significant activation in some of the frontal and parietal areas associated with the attention/ task-positive network as well as in the ACC and in the bilateral fusiform gyrus (see Figure 5.3). An examination of attention/ task-positive network peak voxels as specified by Fox and colleagues (2006; 2005) revealed task-induced bilateral activation in the intraparietal sulcus (IPS) as well as significant unilateral activation in the right superior, middle, and inferior frontal gyri, the right DLPFC, the right supramarginal gyrus, the right precuneus, and the right middle temporal region.

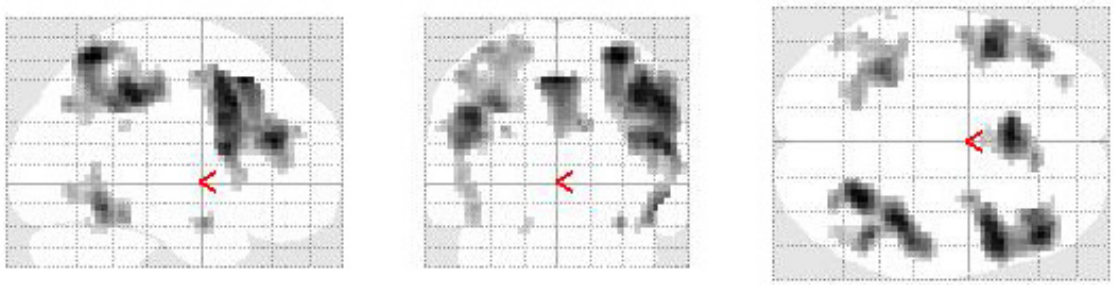

Figure 5.3: Significant voxels found in the whole brain analysis with $p_{FWE} < .05$ (five voxels extent threshold) for the contrast high distracting task irrelevant stimuli minus task relevant stimuli across all participants (24 patients and 24 healthy controls). Clusters of activation can be seen in some areas of the attention/ task-positive network as well as in the ACC and in the bilateral fusiform gyrus.

Comparisons between the group with ADHD and the healthy control group showed no significant whole brain differences. However, ROI analyses yielded a trend for greater activation in the healthy control group compared to the patient group in the right DLPFC ($t_{(46)} = 2.77$, $p_{FWE} = .08$, cluster size: 64 voxels; see Figure 5.4)[11]. No other ROI showed significant or trend level between-group differences. A two sample t-test of the contrast estimates for this cluster showed a significant between-group difference, with the healthy controls showing greater activation than the ADHD patients ($t_{(46)} = 2.57$, $p = .01$; healthy controls: $M = 0.92$, $SD = 0.79$; ADHD: $M = 0.36$, $SD = 0.71$). Correlations of the contrast estimates for this cluster showed no association of mean activity and any of the performance parameters. For the patient group, there were no significant correlations of mean activation of this cluster and any of the CAARS subscales.[12]

[11] See Table 8.3 (appendix) for MNI coordinates of the significant between-group peak voxel difference.

[12] These results remained unchanged when contrast estimates for the peak voxel instead of the cluster were entered into the analyses.

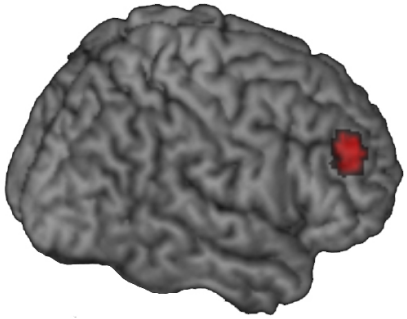

Figure 5.4: Cluster found in the ROI analyses with the trend for greater peak voxel activation for the contrast high distracting task irrelevant minus task relevant stimuli in the healthy control group compared to the patient group in the right DLPFC.

Given the bilateral activation of the fusiform gyrus across all participants, individual activation of the FFA was extracted for high distracting task irrelevant stimuli minus the passive viewing control condition as well as for task relevant stimuli minus the passive viewing control condition. A mixed model ANOVA with the between-subjects factor *group* and the within-subjects factor *task relevance* yielded a significant main effect of task relevance ($F_{(1,46)} = 20.62$, $p < .001$) with high distracting task irrelevant stimuli leading to significantly higher contrast estimates than task relevant stimuli (high distracting task irrelevant stimuli: $M = 0.48$, $SD = 1.82$.; task relevant stimuli: $M = -0.25$, $SD = 1.45$). There was no significant main effect of group and no significant interaction of group and task relevance (both $p > .1$). Interestingly, FFA effect sizes for high distracting task irrelevant stimuli minus task relevant stimuli correlated significantly with mean contrast estimates for the right DLPFC for the same contrast ($r_{(46)} = .35$, $p = .02$): The more activation in the right DLPFC for high distracting task irrelevant compared to task relevant stimuli, the more FFA activation was found for the same contrast.

Correlations of FFA contrast estimates and ADHD symptoms in the patient group showed a trend level correlation of contrast estimates for high distracting task irrelevant minus task relevant stimuli and scores on the CAARS DSM-IV Hyperactive/ Impulsive Symptoms subscale ($r_{(22)} = -.39$, $p = .06$): The higher self-reported symptoms of hyperactivity/ impulsivity, the lower the differential FFA activation for task irrelevant minus task relevant stimuli. In contrast, there were no correlations of the CAARS scales and any of the performance parameters.

5.5.4.2 Patients with ADHD: MPH Medication versus Placebo

(1) Behavioural Data

A mixed model ANOVA with the between-subjects factor *medication* and the within-subjects factor *time of measurement* showed no main effect of medication or of time of measurement and no interaction of medication and time of measurement for any of the behavioural parameters (all $p > .1$; see Table 5.4 for performance parameters of the two groups).

(2) fMRI Data

The peak voxels described under 5.5.4.1 (2) were used for the analysis of medication-induced between-group differences in the patient group. The flexible factorial model as implemented in SPM8 with the between-subjects factor *medication* and the within-subjects factor *time of measurement* yielded no significant interactions between medication and time of measurement for any of the investigated peak voxels. A mixed model ANOVA for individual activation of the FFA with the between-subjects factor *medication* and the within-subjects factors *time of measurement* and *task relevance* yielded a significant main effect of task relevance ($F_{(1,19)} = 8.95$, $p = .007$) with high distracting task irrelevant stimuli leading to significantly higher contrast estimates than task relevant stimuli across all participants and both appointments (high distracting task irrelevant stimuli: $M = 0.46$, $SD = 1.61$; task relevant stimuli: $M = -0.22$, $SD = 1.24$). There were no other significant main effects or interactions (all $p > .1$).

5.5.5 Discussion

Consistent with the results from the previous fMRI study, the experimental task led to bilateral activation of frontal and parietal lobe regions. As expected, the obtained fMRI data showed activation patterns that were very similar to those

obtained in the previous fMRI study. In addition, the results from this larger sample showed significant activation of the ACC. Given the need to control the interference possibly caused by distracting stimuli, this activation is not entirely surprising and consistent with previously reported ACC functions (Bush, Luu, & Posner, 2000). However, while the overall frontal and parietal activation was bilateral, active nodes of the task-positive/ attention network were found mainly in the right hemisphere. This conflicts with our previous results as well as with the literature (Gazzaley et al., 2007; Jha et al., 2004), where the main activation was found to be in the left hemisphere, and cannot be satisfactorily explained at the moment.

As hypothesised, the task-induced network activation was lower in the aADHD group than in the control group, although this was found only for a cluster in the right DLPFC. Contrary to the hypothesis that task-positive network hypoactivation in aADHD might be linearly related to ADHD symptoms, we found no correlation of mean contrast estimates for this cluster and T-scores on any of the CAARS scales. In addition, we could not replicate findings that pointed to an up-regulation of the task-positive network through MPH treatment (Cubillo et al., 2013; Wong & Stevens, 2012). Importantly, there are some differences between the studies reporting these findings and our study. First, these studies investigated children and adolescents, respectively, and there are so far no reports that allow conclusions about the transferability of these findings to adult patients. In addition, both studies used single dose MPH trials or an on/off design, which makes comparisons of the results even more difficult. It furthermore has to be noted that we only investigated the network nodes that showed significant activation across all participants in order to restrict the number of statistical tests. It is therefore possible albeit unlikely that medication effects for some of the network nodes were missed.

As in the previous study, we also found significantly increased individual FFA activation for high distracting task irrelevant compared to task relevant stimuli, which is consistent with the literature (Jha et al., 2004). Interestingly, the differential FFA activation for high distracting task irrelevant stimuli minus task relevant stimuli correlated significantly with the activation of the right DLPFC

cluster for the same contrast. This is comparable to the results from our first (EEG) study, although we did not find a corresponding correlation in the second (fMRI) study, when an activation cluster in the left DLPFC was examined[13]. Furthermore and in contrast to the findings from the EEG study, we found a negative association of FFA contrast estimates for high distracting task irrelevant minus task relevant stimuli and T-scores on the CAARS DSM-IV Hyperactive/ Impulsive Symptoms subscale for the patient group, where higher symptom scores were associated with reduced differences between task relevant and task irrelevant stimuli. Although the exact meaning of these reduced differences is unclear (Jha et al., 2004), these results still point to an impact of aADHD symptoms of visual processing modulation depending on task relevance. Since the sample in the EEG study reported only subclinical ADHD symptoms and overall hyperactive/ impulsive symptoms were in the low normal range (mean T-score: 42.1, standard deviation: 9.7), this effect might likely be only visible in a clinical sample. On a similar but opposite note, ADHD symptoms as assessed with the CAARS did not correlate with any of the performance parameters in this study. Although this is contrary to our hypotheses and to the results of the EEG study, these correlations might only have been visible for the lower overall symptoms of a non-clinical sample.

To conclude, although the experimental task clearly activated the task-positive/ attention network, this activation might not have been strong enough to yield widespread activation differences between the well-matched aADHD patient and healthy control groups and between the ADHD MPH and placebo groups, respectively. Nevertheless, the difference between aADHD patients and healthy controls in the right DLPFC seems to be directly related to the requirements of the experimental task. In addition, while we could replicate some of the results from the first (EEG) study, which examined a subclinical sample, some of the obtained

[13] When this right DLPFC peak voxel was used to re-examine the data from the previous fMRI study, we found a comparable cluster of activation in the associated 9 mm spherical ROI, which also correlated very strongly with individual FFA activation in this sample (cluster size: 110 voxels; peak voxel: $t_{(17)} = 5.30$, $p_{FWE} = .003$; $r_{(16)} = .62$, $p = .01$). This provides further support for the assumption that frontal activation in this area might be directly related to differences in the visual processing of the presented stimuli. However, given the correlational nature of these results no conclusions about causality can be made.

results were contrary to our previous findings. Nevertheless, the main findings of task-related frontal and FFA activation could be replicated and even extended. Correlations furthermore point to the importance of frontal regions in the task-induced modulation of visual processing as well as to a possible impact of clinically important hyperactive/ impulsive symptoms on this modulation. These findings underscore the importance to not rely on findings from samples with subclinical symptoms, but to transfer established paradigms to investigations with clinical populations.

5.6 N-Back Task

As detailed in 5.1, this study's goal was the assessment of functional activation during more global working memory demands in aADHD patients and healthy controls as well as the examination of MPH effects in aADHD patients using an established modification of the classic n-back working memory paradigm (Goldberg et al., 2003). This is particularly interesting, as one of the few studies that investigated working memory functioning using the classic n-back task reports overall decreased activation in the attention/ task-positive network when activation of an aADHD group was compared to a matched control group (Bayerl et al., 2010). Importantly, very few between-group differences were visible when the two groups were compared using whole brain analyses.

We decided to employ a modified variant of this task, which should yield activation patterns similar to and possibly more pronounced than the activation patterns found with the classic n-back task. This modified n-back task had previously been shown to be sensitive to effects of the *COMT* genotype on frontal lobe activation (Diaz-Asper et al., 2008; Egan et al., 2001) as well as to interactions of *COMT* genotype and amphetamine intake in healthy controls (Mattay et al., 2003). It therefore seemed very well suited for the investigation of healthy controls and aADHD patients, the effect of MPH medication and placebo in aADHD patients, and possible interactive effects of *COMT* genotype and ADHD diagnosis.

As described above (see 5.1 and 5.5), the focus in data analysis was again placed on activation of the task-positive network (Banich et al., 2009; Cortese et al., 2012; M. D. Fox et al., 2006; M. D. Fox et al., 2005; Valera et al., 2010) and on its possible up-regulation after stimulant medication intake (Cubillo et al., 2013; Wong & Stevens, 2012).

5.6.1 Hypotheses

1. We expected the 2-back condition of this task to lead to increased activation of frontal and parietal nodes of the attention/ task-positive network compared to the 0-back control condition (Egan et al., 2001).
2. ADHD patients should show hypoactivation in these network nodes (Cortese et al., 2012; Cubillo et al., 2013), and network activation should correlate negatively with ADHD symptoms as reported on the CAARS.
3. Across all participants, we expected activation in the attention/ task-positive network to correlate positively with behavioural performance.
4. In addition, ADHD patients treated with MPH were hypothesised to show higher activation of the attention/ task-positive network at the second fMRI appointment compared to their first appointment and to placebo-treated patients (Cubillo et al., 2013; Wong & Stevens, 2012).
5. Based on previous findings from this task (Mattay et al., 2003; Mier et al., 2010), we furthermore expected *COMT* val/val carriers to show inefficient (i.e. increased) frontal activation compared to val/met and met/met carriers across all participants.
6. As in 5.4, we additionally expected the *COMT* val-allele to be more detrimental to ADHD patients than to healthy controls in a gene-dosage fashion, with patient val/val carriers showing the most inefficient activation patterns.

5.6.2 Experimental Paradigm

This modified version of the n-back task is well established in the literature (Diaz-Asper et al., 2008; Egan et al., 2001; Goldberg et al., 2003; Mattay et al., 2003) and was obtained in 2010 by contacting Professor Weinberger at the National Institute of Mental Health (NIMH). It is a modification of the classic n-back task, where participants have to press a response button whenever a stimulus from "n" trials back is repeated (J. D. Cohen et al., 1994). In Weinberger's version of the task, participants are required to respond on *every* trial by indicating the number (numbers range from 1 to 4) shown "n" trials earlier. The task comprised a 0-back, a 1-back, and a 2-back condition, presented in blocks of 30 seconds each. The 0-back condition serves as control condition as it constitutes a motor equivalent to the 1-back and 2-back conditions, but does not require higher cognitive functions of working memory and interference inhibition. Numbers were presented for 500 ms with 1,500 ms interstimulus interval, leading to a total of 15 number presentations per block. Fifteen blocks (i.e. five blocks per condition) were presented in pseudo-randomised order with the entire experiment lasting around 8 minutes, during which 170 fMRI volumes were acquired.

5.6.3 Participants

At the first fMRI appointment, fMRI data of 34 patients with ADHD were obtained. Two data sets were lost because of technical problems. Two patients had to be excluded after preprocessing of the data because of excessive movement in the scanner (continuous repetitive movements and sudden movement of more than 2 mm, respectively). One patient was excluded because her behavioural performance showed extreme outlier values, resulting in a total of 29 patient data sets for this task. The control group was chosen from the total sample of healthy participants to be comparable (all $p \geq .2$) to the group with ADHD with regard to age, gender, and years of schooling (see Table 5.5 for sample characteristics).

Two more patient data sets were lost at the second fMRI appointment: One patient discontinued the study after the first fMRI appointment for unknown reasons, while a second patient could not participate in the second fMRI appointment due to MRB safety requirements (work in metal processing). This resulted in a total of 27 patient data sets that comprised both the first fMRI appointment without medication and the second fMRI appointment after 6 weeks of MPH or placebo treatment (see Table 5.5).

Table 5.5: Overview of mean demographic data, ASRS scores, and distribution of COMT genotype for both groups for the n-back task. Standard deviation is noted in parentheses unless stated otherwise.

	1st appointment		1st/2nd appointment (ADHD)	
	Controls	ADHD	Placebo	MPH
N-Back				
Participants (male)	29 (13)	29 (18)	13 (7)	14 (9)
Mean age	33.3(*9.3*)	36.1(*9.9*)	36.4(*9.9*)	37.3(*10.1*)
Mean school years	11.1(*1.8*)	10.8(*1.6*)	10.5(*1.5*)	11.4(*1.7*)
StPM raw score	50.7(*4.9*)	49.4(*7.0*)	49.2(*8.2*)	49.6(*6.3*)
Mean inattention[1]	11.2(*4.6*)*	24.0(*4.8*)*	25.3(*4.0*)/22.5(*7.4*)	23.4(*4.9*)/15.9(*7.2*)
Mean hyperactivity	9.7(*5.4*)*	18.7(*6.2*)*	20.5(*5.3*)/17.5(*7.2*)	16.3(*6.3*)/11.4(*6.3*)
COMT genotype				
met/met (male)	7 (3)	6 (6)		
val/met (male)	14 (7)	17 (8)		
val/val (male)	6 (3)	6 (4)		

Note. [1] Symptoms of inattention and hyperactivity/ impulsivity as assessed with the ASRS; * denotes significant between-group differences ($p < .001$).

5.6.4 Results

5.6.4.1 Patients with ADHD versus Healthy Controls

(1) Behavioural Data

Mixed model ANOVAs for correct responses, incorrect responses, and missed trials with the between-subjects factor *group* and the within-subjects factor *task difficulty* yielded no significant main effect of group and no significant interaction of group and task difficulty for correct responses (both $p > .1$). There was, however, a significant main effect of task difficulty ($F_{(2,112)} = 99.37$, $p < .001$) with participants indicating significantly fewer correct responses with increasing task difficulty ($p < .001$ for all post-hoc comparisons). The same was true for missed trials ($F_{(2,112)} = 52.22$, all $p < .001$) and for incorrect responses ($F_{(2,112)} = 47.75$, all $p < .001$, except $p = .01$ for the post-hoc comparison of the 0-back and the 1-back condition; see Table 5.6 for performance parameters of the different groups). As responses in this paradigm were given simultaneously with the continuous appearance of the number stimuli, reaction times do not represent meaningful performance indicators and were therefore not analysed.

Table 5.6: Overview of mean performance for healthy controls and ADHD patients as well as the ADHD placebo and MPH groups in the n-back task. The standard deviation is noted in parentheses.

	1st appointment		1st/2nd appointment (ADHD)	
	Controls	ADHD	Placebo	MPH
0-Back				
% correct	93.9(*7.5*)	94.7(*4.6*)	93.8(*6.0*)/97.4(*3.2*)	95.7(*3.2*)/97.2(*2.1*)
% incorrect	4.7(*6.0*)	4.1(*3.2*)	4.3(*3.7*)/2.2(*2.6*)	4.0(*3.0*)/2.4(*2.1*)
% missed trials	1.3(*2.8*)	1.2(*2.2*)	1.9(*3.1*)/0.4(*0.9*)	0.3(*0.6*)/0.3(*0.6*)
1-Back				
% correct	83.4(*16.6*)	81.2(*17.0*)	79.1(*19.7*)/86.2(*13.2*)	82.1(*15.9*)/84.3(*17.0*)
% incorrect	8.7(*8.8*)	7.1(*6.1*)	7.3(*6.8*)/6.3(*5.3*)	6.9(*6.1*)/8.6(*12.0*)
% missed trials	7.9(*11.9*)	11.7(*14.9*)	13.6(*16.2*)/7.6(*12.6*)	11.0(*14.9*)/7.1(*12.0*)

2-Back

% correct	65.4(*21.3*)	60.8(*20.7*)	63.5(*21.6*)/70.9(*17.0*)	59.3(*21.7*)/69.8(*18.0*)
% incorrect	18.3(*14.3*)	17.0(*12.0*)	16.4(*9.8*)/20.0(*24.7*)	16.0(*13.8*)/15.0(*11.2*)
% missed trials	16.3(*14.7*)	22.2(*19.2*)	20.1(*20.7*)/13.7(*17.9*)	24.8(*19.6*)/15.2(*16.6*)

Note. There were no significant between-group differences (all $p > .1$). All participants indicated significantly fewer correct and more incorrect responses and missed more trials with increasing task difficulty (all $p \leq .01$). ADHD patients indicated significantly more correct responses and missed significantly fewer trials (for the 1-back and 2-back conditions only) at the second compared to the first appointment (all $p < .05$).

(2) fMRI Data

Across all participants, whole brain analyses with $p_{FWE} < .05$ for the contrasts 1-back minus 0-back and 2-back minus 0-back showed very similar activation patterns of the attention/ task-positive network as well as of the cerebellum and the caudate nuclei (see Figure 5.5). This activation was lower in the 1-back contrast than in the 2-back contrast and the contrast 2-back minus 1-back showed increased activation in frontal and parietal areas for the 2-back condition. Therefore, only the contrast of the most demanding condition (2-back) minus the control condition (0-back) was further analysed.

An examination of attention/ task-positive network peak voxels as specified by Fox and colleagues (2006; 2005) revealed task-induced bilateral activation in the IPS, the inferior parietal lobule, and the DLPFC as well as significant unilateral activation in the right superior, middle, and inferior frontal gyri, the right supramarginal gyrus, the right precuneus. These peak voxels were subsequently examined for between group differences as specified in 5.2.3.

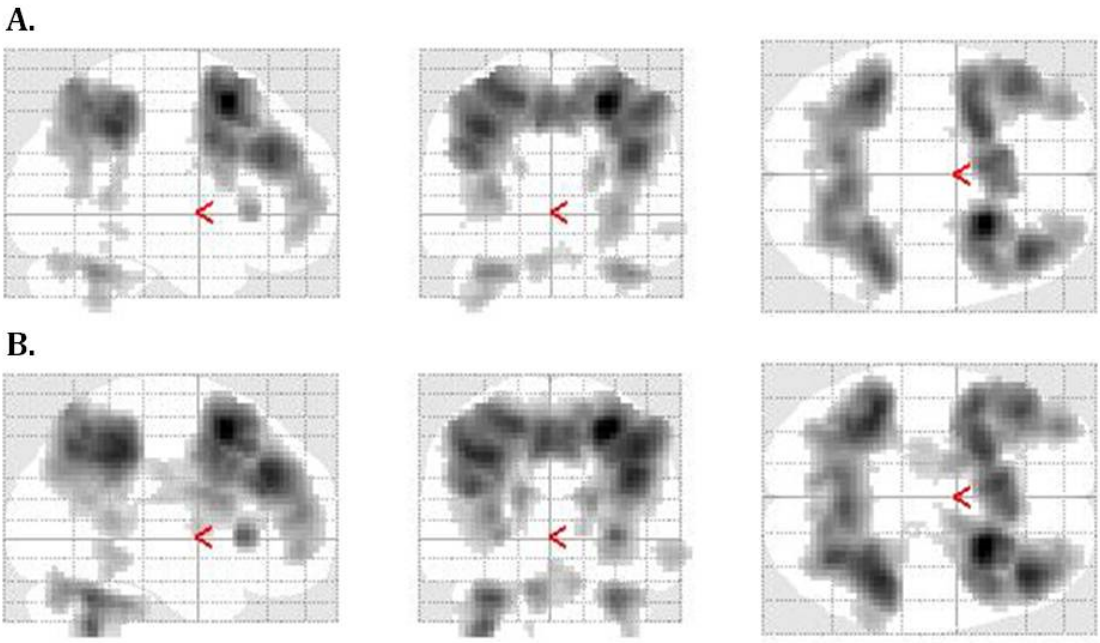

Figure 5.5: Significant voxels found in the whole brain analysis with $p_{FWE} < .05$ (five voxels extent threshold) for the contrast 1-back minus 0-back (A.) and the contrast 2-back minus 0-back (B.) across all participants (29 patients and 29 healthy controls). Clusters of activation can be seen in areas of the attention/ task-positive network as well as in the cerebellum and in the caudate nucleus.

Comparisons between the group with ADHD and the healthy control group showed no significant whole brain differences, but ROI analyses yielded significantly greater peak voxel activation in ADHD patients compared to healthy controls in the left anterior IPS ($p_{FWE} = .02$), the right inferior/middle frontal gyrus (IFG/MFG; $p_{FWE} = .050$), and the left DLPFC ($p_{FWE} = .03$; see Figure 5.6 and Table 5.7). In addition, we found trends for greater activation in the patient group compared to the healthy controls in the right posterior IPS and the right anterior IPS ($p_{FWE} = .06$ and $p_{FWE} = .09$, respectively; see Table 5.7 for cluster sizes).

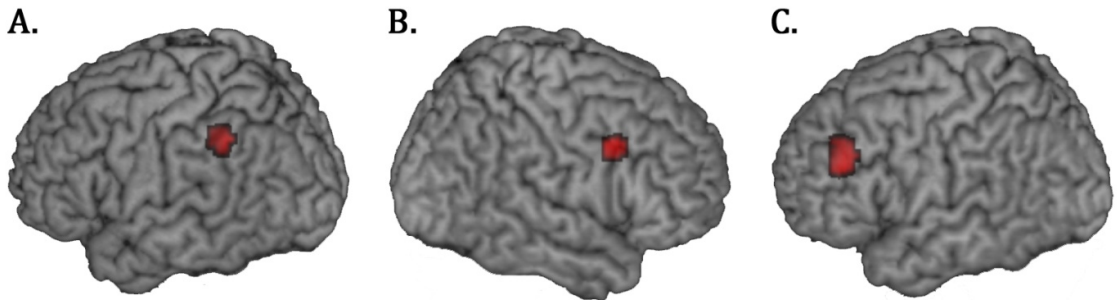

Figure 5.6: Clusters found in the ROI analyses with significantly greater peak voxel activation for the contrast 2-back minus 0-back in the patient group compared to the healthy controls in the left anterior IPS (A.), the right IFG/MFG (B.), and the left DLPFC (C.).

Two sample t-tests of the contrast estimates for the clusters that contained a trend level or significant peak voxel difference also showed significant between-group differences with the ADHD patients showing consistently greater activation than the healthy controls (see Table 5.7 for relevant statistics by anatomical region).

Table 5.7: Anatomical regions with significant peak voxel between-group differences with corresponding cluster sizes (in voxels) and p_{FWE}-values of the peak voxel difference, as well as means and standard deviations (SD) of the contrast estimates for the respective clusters for the two groups (healthy controls (HC) and ADHD patients), and the t- and p-values of the corresponding uncorrected two-sample t-tests.

Anatomical region	Cluster size	p_{FWE}	Mean contrast estimates (SD)		*t*-value[1]	*p*
			HC	ADHD		
Left anterior IPS	43	.02	0.44(0.*29*)	0.66(*0.35*)	2.51	.02
Right IFG/MFG	41	.050	0.33(*0.28*)	0.53(*0.28*)	2.68	.01
Left DLPFC	86	.03	0.28(*0.26*)	0.49(*0.37*)	2.72	.009
Right posterior IPS	19	.06	0.19(*0.50*)	0.47(*0.41*)	2.31	.03
Right anterior IPS	57	.09	0.51(*0.32*)	0.73(*0.39*)	2.37	.02

Note. [1] degrees of freedom (df) = 56.

To compute meaningful correlations with performance data, performance indices were calculated as the ratio of *2-back % correct responses* to *0-back*

% correct responses. To avoid missing values for the incorrect response ratios due to no incorrect responses in any of the two conditions, *% incorrect responses* was transformed into its corresponding negative *% not incorrect responses* (100 % minus *% incorrect responses*). This procedure yielded two different performance indices, one based on the number of correct responses and the other based on the number of incorrect responses in the two examined conditions. The index based on correct responses should be seen as indicating performance quality, with higher values reflecting better behavioural performance. In contrast, the index based on incorrect responses should be understood as indicating performance monitoring, since it signals how many incorrect responses were given before the participant realised that he or she was making a mistake. As the percentage of incorrect responses was transformed to its negative for the following calculations, higher values reflect better behavioural performance for this index. Correlations were calculated for these performance ratios and the contrast estimates for the clusters specified above.

These calculations revealed significant or trend level associations between correct response performance and activation in the left anterior IPS, as well as the right anterior and posterior IPS: The higher the activation in these areas, the better performance with regard to correct responses. Similarly, incorrect response performance correlated significantly with activation in the right IFG/MFG as well as the right anterior and posterior IPS: The higher the activation in these areas, the fewer incorrect responses were given (see Table 5.8 for all correlations). There were no significant correlations for the left DLPFC (both $p > .1$). For the patient sample, activation in some of the investigated areas furthermore correlated with symptom severity as measured with the CAARS. Higher fMRI contrast estimates in the left anterior IPS, the right IFG/MFG, and the right posterior IPS correlated significantly with scores on the CAARS DSM-IV Hyperactive/ Impulsive Symptoms scale. In addition, these areas also showed significant correlations with the CAARS DSM-IV Total ADHD Symptoms scale (see Table 5.8 for all correlations).

Table 5.8: Correlation coefficients (r) and p-values for the contrast estimates and the two performance indices for the entire sample, as well as correlation coefficients (r) and p-values for the contrast estimates in these clusters and T-scores for CAARS DSM-IV Hyperactive/ Impulsive Symptoms scale and CAARS DSM-IV Total ADHD Symptoms scale for the patient sample.

Anatomical region	Performance (correct) *r* (*p*-value)[1]	Performance (incorrect) *r* (*p*-value)[1]	CAARS Hyper./Impuls. *r* (*p*-value)[2]	CAARS Total Sympt. *r* (*p*-value)[2]
Left anterior IPS	.25 (.06)	.22 (n.s.)	.46 (.01)	.54 (.002)
Right IFG/MFG	.20 (n.s.)	.32 (.01)	.41 (.03)	.44 (.02)
Right posterior IPS	.35 (.01)	.48 (<.001)	.46 (.01)	.40 (.03)
Right anterior IPS	.24 (.07)	.37 (.004)	.28 (n.s.)	.40 (.03)

Note. [1] df = 56; [2] df = 27.

5.6.4.2 Patients with ADHD: MPH Medication versus Placebo

(1) Behavioural Data

Mixed model ANOVAs for correct responses, incorrect responses, and missed trials with the between-subjects factor *medication* and the within-subjects factors *time of measurement* and *task difficulty* showed significant main effects of time of measurement ($F_{(1,25)} = 9.14$, $p = .01$) and task difficulty ($F_{(2,50)} = 59.41$, $p < .001$) for correct responses: All participants indicated significantly fewer correct responses with increasing task difficulty ($p < .001$ for all post-hoc comparisons) and showed better performance at the second compared to the first fMRI appointment ($p = .01$). The same was true for missed trials (main effect time of measurement: $F_{(1,25)} = 12.67$, $p = .002$; main effect task difficulty: $F_{(2,50)} = 23.52$, $p < .001$), which also showed a significant interaction of time of measurement and task difficulty ($F_{(2,50)} = 8.65$, $p = .001$): Paired t-tests showed a significant decrease of missed trials at the second compared to the first fMRI measurement for the 1-back condition ($p = .02$) and the 2-back condition ($p < .001$), but not for the 0-back condition ($p = .14$). In contrast, for incorrect responses only a main effect of task

difficulty could be found ($F_{(2,50)} = 24.45$, $p < .001$): Participants gave significantly fewer incorrect responses in the 0-back condition compared to the 1-back condition ($p = .01$) and the 2-back condition ($p < .001$), which were also significantly different ($p = .001$). There were no other significant main effects or interactions (all $p > .1$; see Table 5.6 for performance parameters of the two groups at the second appointment).

(2) fMRI Data

The peak voxels described under 5.6.4.1 (2) were used for the analysis of medication-induced between-group differences in the patient group. Comparisons between the MPH and the placebo group yielded no significant whole brain differences. However, ROI analyses showed a significant interaction of medication and time of measurement for the contrast 2-back minus 0-back in the right SFG ($F_{(1,25)} = 14.14$, $p_{FWE} = .04$, cluster size: 12 voxels; see Figure 5.7).

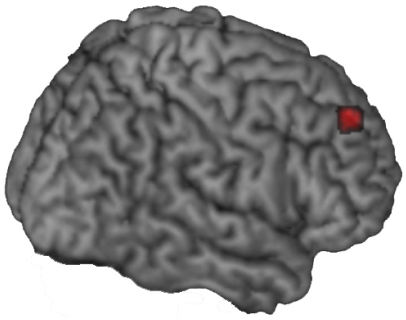

Figure 5.7: Cluster found in the ROI analyses for the interaction of medication and time of measurement for the contrast 2-back minus 0-back in the right superior frontal gyrus.

Subsequent two-sample t-tests as implemented in SPM8 showed a trend for greater activation of the MPH group compared to the placebo group ($t_{(25)} = 2.81$, $p_{FWE} = .09$, cluster size 15 voxels) at the second fMRI appointment, which was not present ($p > .1$) at the first appointment. A mixed model ANOVA of the contrast estimates for this cluster also yielded a significant interaction of medication and time of measurement ($F_{(1,25)} = 11.25$, $p = .003$). Post-hoc t-tests showed significantly higher activation for the MPH group compared to the placebo group at

the second fMRI appointment ($t_{(25)}$ = 2.18, p = .04) with no significant between-group difference at the first appointment (p > .1). In addition, paired-sample t-tests showed a trend for an activation decrease in the placebo group ($t_{(12)}$ = 2.06, p = .06), while the MPH group showed a significant increase in activation ($t_{(13)}$ = 2.97, p = .01) between the two fMRI appointments (see Figure 5.8).

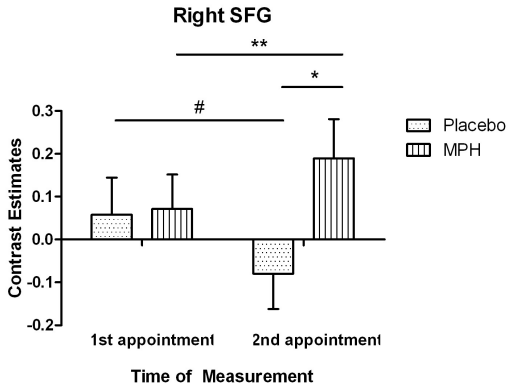

Figure 5.8: Mean contrast estimates for the cluster with peak voxel interaction for the two groups (MPH and placebo) by group and time of measurement for the contrast 2-back minus 0-back. Note. *p ≤ .05, **p ≤ .01; #p ≤ .1.

5.6.4.3 Interaction of *COMT* Genotype and ADHD Diagnosis

(1) Behavioural Data

Two healthy control participants had to be excluded from this investigation because the analysis of their DNA yielded inconclusive findings for *COMT* genotype. The non-parametric equivalents of the two-way ANOVA (as described in 5.2.4) with the between-subjects factors ADHD and *COMT* genotype showed no significant main effects of ADHD or *COMT* genotype and no significant interaction for correct responses, incorrect responses, or missed trials for any of the three conditions (all p > .1). The effect of task difficulty could not be investigated using non-parametric methods. However, parametric mixed model ANOVAs which included task difficulty as a within-subjects factor showed no significant interactions involving *COMT* genotype for correct responses, incorrect responses, or missed trials (all p > .1).

(2) fMRI Data

We exploratorily examined the contrast estimates of the clusters showing between-group differences for possible interaction effects of *COMT* genotype and ADHD diagnosis using the non-parametric equivalent of the two-way ANOVA described in 5.2.4. For the contrast 2-back minus 0-back, activation in the left anterior IPS showed a significant main effect of *COMT* genotype ($F_{(2,50)} = 4.44$, $p = .02$) with val/val carriers displaying significantly greater activation than val/met carriers across all participants ($p = .01$; val/met: $M = 0.48$, $SD = 0.33$; val/val: $M = 0.74$, $SD = 0.31$). In addition, there was a significant interaction of *COMT* genotype and ADHD ($F_{(2,50)} = 4.88$, $p = .01$): ADHD patients with val/met genotype showed significantly greater contrast estimates in the investigated area than healthy controls with this genotype ($p = .001$) and ADHD patients with val/val genotype also showed a trend for greater activation than healthy val/val controls ($p = .07$; see Figure 5.9).

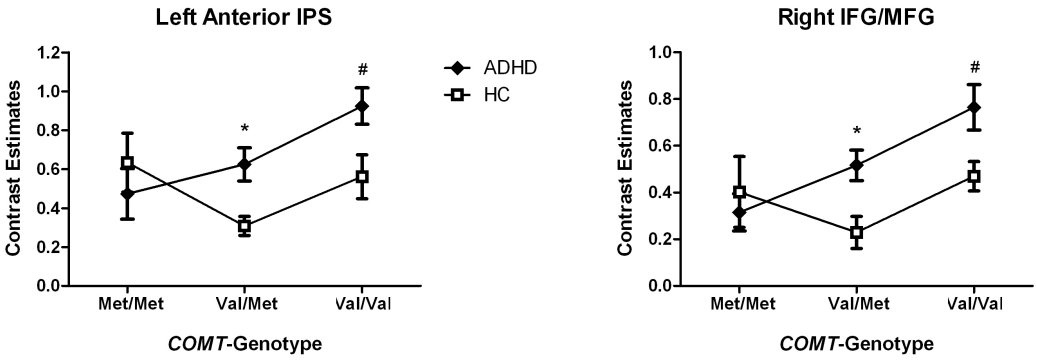

Figure 5.9: Mean contrast estimates for the left anterior IPS and in the right IFG/MFG for patients with ADHD and healthy controls and the different COMT genotypes. Error bars denote standard error of the mean (SEM). Significant between-group differences ($p \leq .05$) are marked by *, trends ($p \leq .1$) are marked by #.

Contrast estimates for the right IFG/MFG also showed a significant main effect of *COMT* genotype for the contrast 2-back minus 0-back ($F_{(2,50)} = 4.11$, $p = .02$), with val/val carriers displaying significantly greater activation than val/met carriers ($p = .03$) and than met/met carriers across all participants

(p = .04; val/val: M = 0.62, SD = 0.25; val/met: M = 0.39, SD = 0.30; met/met: M = 0.36, SD = 0.31). In addition, there was a significant interaction of *COMT* genotype and ADHD ($F_{(2,50)}$ = 3.65, p = .03): ADHD patients with val/met genotype showed significantly greater contrast estimates in the investigated area than healthy controls with this genotype (p = .01). In addition, ADHD patients with val/val genotype showed a trend for greater activation than healthy val/val controls (p = .07; see Figure 5.9).

Within-groups, ADHD met/met carriers displayed significantly or trend level lower activation in both areas compared to ADHD val/val carriers (left anterior IPS: p = .07; right IFG/MFG: p = .009), while activation in these two COMT groups was the same in the healthy control group (both p > .1). There was no main effect of *COMT* genotype or interaction of *COMT* genotype and ADHD for any of the other investigated areas.

5.6.5 Discussion

The results from this study extend the findings from the selective attention task and from the literature in an interesting and unexpected way. First of all, the most demanding 2-back condition was hypothesised to cause increased activation of the attention/ task-positive network compared to the 0-back condition, which served as a motor control condition. This hypothesis was confirmed, with the 1-back and the 2-back task showing a substantial and parametric increase in network activation over the 0-back condition. However, based on a meta-analysis of fMRI studies investigating EF (Cortese et al., 2012), we hypothesised to find a hypoactivation of these network nodes in aADHD patients compared to healthy controls. This was not the case and the data did indeed show a hyperactivation of several network nodes in the frontal and parietal lobes when the ADHD group was compared to the control group.

In order to interpret this finding, the results from the meta-analysis as well as from two other similar studies need to be re-examined. One similar study employed a classic n-back task and reports hypoactivation particularly in the

DLPFC in a group of children with ADHD compared to healthy controls (Cubillo et al., 2013). These two groups showed behavioural performance differences, with the ADHD group performing significantly worse than the healthy control group in the more demanding conditions. The same is true for a study with aADHD patients, which reports less network activation but also worse performance in the patient group (Bayerl et al., 2010). Interestingly, the meta-analysis of fMRI studies with children and adolescents reports hypoactivation in the frontoparietal/ task-positive network with hyperactivation only in not task-related networks (Cortese et al., 2012). In contrast, the fMRI studies of adults showed hypo- as well as hyperactivation in attention/ task-positive networks, which the authors interpreted as possibly reflecting compensatory efforts in the affected networks. This interpretation is very compatible with our own data: While the hyperactivation of the task-positive network in the aADHD patients was unexpected, network activation correlated positively with behavioural task performance based on both correct and incorrect responses across all participants. This supports the interpretation of the ADHD group's hyperactivation serving compensatory purposes since increased activation was indeed associated with better performance and – importantly – there were no behavioural performance differences between the two groups. In addition, network activation correlated positively with the CAARS Hyperactive/ Impulsive and Total ADHD Symptoms scales in aADHD patients. This might indicate that aADHD patients with more severe symptoms had to apply more effort to successfully complete the task, which would further support the interpretation of increased functional activation reflecting compensatory efforts.

Furthermore, we found a hypothesised increase of activation in the right SFG of patients treated with MPH, which was significant compared to their first fMRI measurement without medication as well as to placebo-treated patients. This is in line with previous reports of MPH up-regulating network activity and frontal activation (Cubillo et al., 2013; Wong & Stevens, 2012). The investigation of possible effects of *COMT* genotype and ADHD diagnosis on the network nodes showing between-group differences moreover yielded main effects of *COMT* in frontal as well as parietal regions of interest, with val/val carriers showing more

inefficient activation than the other genotype groups. While the effect of *COMT* on frontal lobe functioning is in line with many previous findings (Egan et al., 2001; Mattay et al., 2003; Mier et al., 2010), less is know about its impact on parietal lobe functioning. There is, however, some indication that *COMT* might similarly be linked to activation changes in the posterior parietal cortex as in the frontal cortex if a task requires rapid updating of information (Tan et al., 2007). Interestingly, the two regions with main effects of *COMT* genotype on activation also showed an interactive effect of *COMT* genotype and ADHD diagnosis. Contrary to previous results, healthy controls showed no differences between the genotype groups in the frontal ROI and val/met carriers showed the most efficient activation in the parietal ROI. In contrast, ADHD patients with two met-alleles displayed the most efficient activation in both ROIs and efficiency showed a linear decrease with val/val carriers being the most inefficient. This is in line with our hypothesis and might point to a left shift in the cortical dopaminergic response function caused by the combined effects of *COMT* genotype and ADHD (Arnsten, 2006; Pliszka, 2005). Still, it should be kept in mind that cell sizes for the investigation of this interactive effect were rather small and further important differences might have been missed. Nevertheless, the preliminary results obtained in this study point to the possibility of an interesting interaction of *COMT* genotype and ADHD diagnosis, which warrants further investigation.

6 Concluding Discussion

6.1 Selective Attention and Working Memory

A main focus of the studies presented in this dissertation was the investigation of selective attention functions mediated by the working memory central executive (Baddeley, 2012; J. D. Cohen et al., 2000; Postle, 2006). Similar to previous studies, we found support for the hypothesis that the central executive modulates early visual processing based on how relevant a stimulus is for successful task completion (Egner & Hirsch, 2005; Gazzaley et al., 2005; Polk et al., 2008; Rutman et al., 2010; Schreppel et al., 2008; Sreenivasan & Jha, 2007; Zanto & Gazzaley, 2009) in both the first (EEG), and the second and third (fMRI) studies. Our results also support previous investigations that took the degree of distractibility of the task irrelevant stimulus into consideration (Jha et al., 2004; Sreenivasan & Jha, 2007).

Both EEG and fMRI showed differential visual processing of stimuli that were high distracting compared to stimuli that were low distracting. While high distracting task irrelevant stimuli led to reduced N170 amplitudes compared to low distracting task irrelevant stimuli and compared to task relevant stimuli in the EEG study, FFA activation for high distracting task irrelevant stimuli was found to be increased in the fMRI studies. This increase is more difficult to interpret than the decreased amplitudes in the EEG study, as it might reflect inhibitory processes, increased maintenance efforts, or simply additive presentation effects in this area (Jha et al., 2004; Ranganath & Paller, 1999; Rossion et al., 2004). However, the results of the second (fMRI) study also showed possibly increased activation – achieving trend level significance before correcting for multiple comparisons – when the low distracting task irrelevant stimulus was from another category than the task relevant stimulus. As FFA activation was still increased when the maintained task relevant stimulus was from another category (house) in the low distracting task irrelevant condition, this most likely supports the interpretation of the increased BOLD response reflecting inhibitory processes in the FFA. It furthermore contradicts additive effects caused by the presentation of a high

distracting task irrelevant face stimulus while a relevant face stimulus was being maintained in working memory. However, to further disentangle possible interpretations of the differential processing observed in both EEG and fMRI, it would be necessary to try to include high distracting task irrelevant stimuli from a separate category in the experimental paradigm, although that might admittedly be difficult to accomplish.

In addition, previous reports of frontal involvement in processing modulation and recovery from interference could be replicated (Gazzaley et al., 2007; Jha et al., 2004; K. Kessler & Kiefer, 2005). Both EEG and fMRI data showed a processing enhancement for high distracting task irrelevant stimuli compared to task relevant stimuli in frontal areas. While the EEG results showed no laterality effects, fMRI data from the third study strongly implicated the right hemisphere. Differential activation for task relevant minus high distracting task irrelevant stimuli in a right DLPFC cluster belonging to the task-positive network (M. D. Fox et al., 2006; M. D. Fox et al., 2005) correlated significantly with FFA activation for the same contrast. This might be further indication of inhibitory processes in the FFA being coordinated by the DLPFC, especially as a cluster in the same region of interest was found to show comparable correlations in a post-hoc analysis of data from the second (fMRI) study.

The selective attention paradigm furthermore proved sensitive to the detection of both aADHD and *COMT* effects in the research presented above. The ADHD effects, however, did not transfer as expected from participants with subclinical ADHD symptoms to patients meeting full diagnostic criteria of ADHD: While participants' scores on the CAARS Hyperactive/ Impulsive and Total ADHD Symptoms scales correlated negatively with performance accuracy in the first (EEG) study – which was caused by lower target detection rates – no comparable correlations were found for the patient sample in the third study. Although performance was generally high in both of these studies, a closer inspection of the behavioural data showed significantly higher accuracy, target detection, and faster reaction times in participants from the first compared to the third study, with only the number of false alarms being comparable. This might be due to a number of factors. The most likely explanation for this difference concerns the investigated

samples: While ADHD patients and their matched healthy controls were recruited from a wide range of age and educational backgrounds, the participants with subclinical ADHD symptoms in the first study were mainly students in their twenties. It is therefore possible that the task was only able to tax the impact of ADHD symptoms on performance in the first sample, where the overall level of cognitive functioning was very high. Participants in the fMRI study may also have been more fatigued as they had already completed another task when they performed the selective attention task. It is furthermore possible that the supine position in the fMRI scanner might have contributed to increased drowsiness and thereby worse performance than the seated position in the EEG.

The different sample characteristics might furthermore have influenced the correlations between task-related activation and ADHD symptoms that were observed in the two studies. As ADHD had previously been connected to impaired distractor suppression and executive control (Dramsdahl et al., 2011; Friedman-Hill et al., 2010), it was hypothesised that participants with higher (subclinical) ADHD symptoms would show less differential processing of task relevant and high distracting task irrelevant stimuli. This was not found in the first (EEG) study, where ADHD symptoms on the CAARS DSM-IV Hyperactive/ Impulsive and Total ADHD Symptoms scales correlated negatively only with the N170 amplitudes for the less demanding conditions (low distracting task irrelevant and passively viewed stimuli). In contrast, ADHD patients in the third study showed the expected correlation when FFA activation was examined: The higher patients scored on the CAARS DSM-IV Hyperactive/ Impulsive Symptoms scale, the lower their differential FFA activation for high distracting task irrelevant minus task relevant stimuli. As with the behavioural data above, the high-functioning participants with subclinical ADHD symptoms in the first study might have been able to completely compensate for their symptoms in the two most demanding conditions (task relevant and high distracting task irrelevant stimuli, respectively). In contrast, the patient sample in the third study reported much higher overall symptoms and although behavioural performance was still comparable to that of healthy controls, a complete compensation of their deficits might not have been possible. This lack

of compensation seems to be especially true for those patients with high hyperactive/ impulsive symptoms of ADHD.

6.2 Adult ADHD, Methylphenidate, and *COMT* Genotype

A second focus of this dissertation was the investigation of the effects of MPH on several parameters of EF and working memory. The medication effect on ADHD symptoms found in the third (double-blind placebo-controlled) study corresponded to what would be expected based on previous research. There was only a trend level effect of MPH when response rates and mean score reduction percentages were analysed, which is likely attributable to the size of the investigated sample. Notably, the effect size for between-group differences in response rate[14] was small to medium (d = .46). This is comparable to the results of a larger study, which reports effect sizes between .38 and .62 for different MPH doses (Medori et al., 2008). However, compared to studies solely investigating medication response (Biederman, Mick, et al., 2010; Medori et al., 2008; Spencer et al., 2005), the sample size of our much more time-consuming combined fMRI medication study was necessarily relatively small. Correspondingly, the power to detect a truly existing difference in response rates was only 36 %.

The obtained results were similar when questionnaire scores instead of response rates were considered: Both the MPH and the placebo group showed a decrease in self-reported ADHD symptoms before the second fMRI appointment. Although the MPH group reported trend level lower hyperactivity/ impulsivity scores than the placebo group, this was significant across both appointments and did not interact with the time of measurement. Inspection of the questionnaire scores, however, again points to medication effects in the expected direction.

[14] As described above, medication response was defined as a minimum reduction of 20 % in T-scores on the CAARS DSM-IV Total ADHD Symptoms scale as well as on either the CAARS DSM-IV Inattentive Symptoms scale and/or the CAARS DSM-IV Hyperactive/ Impulsive Symptoms scale from day 1 to day 42.

Therefore, interaction effect sizes (Cohen's *f*) were calculated as described in 5.4.4 to explore whether the sample size was sufficient to detect significant effects of MPH treatment compared to placebo over time. Unfortunately, achieved power was low for the CAARS DSM-IV Inattentive (*f* = .21, power = .42) and DSM-IV Total ADHD Symptoms scales (*f* = .14, power = .25). It is therefore possible that small to moderate interaction effects for these scales were missed due to the insufficient sample size. Estimated effect size was too small to accurately investigate achieved power for the CAARS DSM-IV Hyperactive/ Impulsive Symptoms scale and hence no power calculation could be performed. However, patients' initial scores on the Hyperactive/ Impulsive Symptoms scale were substantially lower than for the other two CAARS scales and mean T-scores on this scale were in the normal range for all patients at the end of the trial. In contrast, power was high for the ASRS inattention subscale (*f* = .25, power = .97), with slightly lower power for the ASRS hyperactivity/ impulsivity subscale (*f* = .23, power = .65). It can therefore be assumed that sample size was sufficient for these questionnaires and statistical analyses should have detected any truly existing interaction effects.

To summarise, a placebo effect on all symptoms of ADHD was found, with patients reporting a significant improvement of their symptoms irrespective of the actual pharmacological treatment they had received. This placebo effect might in part be attributable to the extensive clinical care all patients were engaged in during the course of the study. Furthermore, the sample size was unfortunately insufficient to detect any significant interaction effects for the CAARS DSM-IV Inattentive and DSM-IV Total ADHD Symptoms scales. It might therefore be quite possible to find effects for these subscales with a substantially larger sample (e.g. 84 participants would be necessary to achieve an experimental power of .80 for the CAARS DSM-IV Inattentive Symptoms scale). It should be noted, however, that the achieved response rates of 40 % (placebo group) versus 63 % (MPH group) were very comparable to those reported by much larger clinical trials (Biederman, Mick, et al., 2010; Medori et al., 2008; Rösler et al., 2009). Unlike hypothesized, performance on the neuropsychological tests (particularly on the Stroop *Color Word Test* and the *Digit Span Forward* subtest) was also not influenced by

medication in the patient sample, which might mainly be attributable to the characteristics of these tests.

Several additional points need to be considered when evaluating the response to stimulant medication. First, many studies defined response rates based on symptoms ratings provided by clinically trained investigators (e.g. Biederman, Mick, et al., 2010; Medori et al., 2008; Spencer et al., 2005). A recent meta-analysis identified this practice as problematic due to the risk of blinding failures, caused by trained clinicians' ability to deduce patients' true medication from the behavioural and hemodynamic effects of MPH much better than the patients themselves (Castells et al., 2013). In contrast, the described results from our study rely on patient self-report, which is known to lead to less robust effects (Medori et al., 2008). It should be noted, however, that we defined response rates as a minimum reduction of 20 % in T-scores on the CAARS DSM-IV Total ADHD Symptoms scale as well as on either the CAARS DSM-IV Inattentive Symptoms scale and/or the CAARS DSM-IV Hyperactive/ Impulsive Symptoms scale from day 1 to day 42. This definition is rather liberal, as other studies assumed a minimum reduction of 30 % (in observer ratings) to classify responders (e.g. Biederman, Mick, et al., 2010). Another potential difference in our study pertains to the titration and dose of the dispensed medication. While many of the studies mentioned above use daily MPH doses up to the maximum specified by the manufacturer, medication was titrated more clinically valid and thereby more conservatively in our study, with a maximum weekly increase of 10 mg up to a maximum daily dose of 60 mg. This is well below the maximum recommended daily dose of 1 mg/kg and 80 mg, respectively, for adults (MEDICE Arzneimittel Pütter GmbH & Co. KG). It is therefore possible that a further increase of dosage might have improved eventual response rates – although possibly at the cost of increased side effects.

The fact that medication doses were significantly lower for patients in the MPH compared to the placebo group in our study might be potentially problematic. This difference might have provided the psychiatrists responsible for the titration of the medication with some clues regarding the assigned treatment condition. It should be pointed out, however, that – contrary to other medication trials – no

medically responsible personnel was involved in the collection of any neuropsychological or fMRI data, thereby limiting any impact on the collected data which might have been caused by blinding failures.

Although the selective attention task showed some sensitivity to both aADHD and *COMT*, these effects were more pronounced in the modified n-back task, a more traditional measure of working memory functioning. Like the selective attention task, this task caused a pronounced activation of the task-positive network. We detected robust activation increases in frontal and parietal areas, but also in the cerebellum and in the caudate nucleus, when the most demanding condition was compared to the control condition. However, none of these areas showed any significant activation differences between aADHD patients and healthy participants when univariate whole brain analyses were examined. This is in line with previous reports (Bayerl et al., 2010) and points to rather subtle between-group differences on a network level (Cortese et al., 2012; Cubillo et al., 2013).

Contrary to our hypotheses, we found increased task-positive network activation in the aADHD patients when frontal and parietal nodes of this network were analysed. Nonetheless, a closer examination of the obtained results showed some noteworthy properties of our data. Contrary to a comparable study that reports network hypoactivation in the aADHD sample (Bayerl et al., 2010), we found no behavioural performance differences between the two groups. In addition, task-positive network activation showed a positive correlation with behavioural performance, and activation correlated positively with CAARS Hyperactive/ Impulsive and Total ADHD Symptoms within the patient sample in our study. This combination of results led us to interpret the increased activation in the aADHD patients as compensatory efforts compared to healthy controls, a possibility that was also raised by a previous meta-analysis, which found increased activation of aADHD patients in some of the investigated network nodes (Cortese et al., 2012). Interestingly, the ability to compensate for deficits by increasing network activation seems to be typical in adult patients, as studies with ADHD children consistently showed hypoactivation in task-related networks (Cortese et al., 2012; Cubillo et al., 2013). In addition, we found MPH to further increase frontal activation during task performance, which is also in line with previous

reports (Cubillo et al., 2013; Wong & Stevens, 2012). These results indicate that future studies should place a stronger focus on behavioural task performance of the investigated groups, as this could be the key to whether hypo- or hyperactivation of the investigated networks will be observed when the two groups are compared.

We also found a noteworthy interaction of *COMT* genotype and ADHD diagnosis in both the imaging and the neurophysiological data, which pointed to an additional negative impact of ADHD on the typical neuropsychological and functional activation profiles associated with the *COMT* genotype: Contrary to healthy controls, patients with aADHD showed no advantage for met/met carriers on a stable neuropsychological measure of working memory and no advantage for val/val carriers on a flexible neuropsychological measure of working memory. When functional activation was examined during the modified n-back task, aADHD patients showed a more pronounced negative effect of the *COMT* val-allele on activation efficiency than the healthy control group. These results point to a possible left shift in the inverted U-shaped cortical dopaminergic response function (Bellgrove et al., 2005; Cools & D'Esposito, 2011; Mattay et al., 2003) in aADHD: While healthy controls showed no genotype differences or a slight advantage for the val/met genotype (in the IPS), effects were more pronounced in the aADHD group with the most efficient functioning visible in met/met carriers. This finding has notable implications for research on the response to stimulant medication in aADHD (which could not be investigated here due to insufficient participant numbers per cell). Since some of the investigated parameters showed most efficient functioning in met/met aADHD patients but in val/met healthy controls, this left shift in the response function of aADHD patients might cause met/met patients to be even more sensitive to pharmacologically induced increases of cortical and subcortical dopamine than healthy controls. As a consequence, this group might show a more unfavourable response to stimulants than what was previously observed in healthy met/met carriers (Mattay et al., 2003). This is in line with pharmacogenetic studies, which report a reduced response to stimulant medication in ADHD children with two met-alleles (Cheon et al., 2008; Kereszturi et al., 2008; McGough et al., 2009).

It should be noted, however, that contrary to previous research using this paradigm (Barnett et al., 2008; Egan et al., 2001; Goldberg et al., 2003) we did not find differences in frontal cortical activation for the different *COMT* genotypes in healthy controls. This discrepancy might have been caused by the small sample size, or it might be due to the fact that the investigated ROIs were pre-specified based on task-positive network nodes that had shown between-group differences for healthy controls and aADHD patients. Most importantly, these ROIs were not selected based on previous investigations of the *COMT* genotype. Still, this might make the findings even more relevant, as they indicate an adverse effect of the val-allele on task-positive network nodes that are also affected by ADHD.

6.3 Limitations

There are several limitations to the studies presented in this dissertation. One important limitation concerns the design of the selective attention task. While this design was well suited for investigation with EEG and yielded robust results with this method, it might have been too restrictive for application in an fMRI study. The necessary alternating presentation of task relevant and task irrelevant stimuli considerably reduced the efficiency of this design for the fMRI studies. Combined with the comparably short interstimulus intervals, this alternating presentation contributed to a reduced orthogonality of several of the regressors in the general linear model, thereby limiting the contrasts that could be meaningfully investigated.

For future studies, the design might be improved in one of two ways: First, it might be advisable to abandon the strictly alternating stimulus presentation and to possibly further increase the interstimulus intervals between stimuli from the same condition. However, these modifications would increase task difficulty considerably, as participants would have to maintain the task relevant stimuli in working memory for very long durations. A second – and probably preferable option – would be to change the experimental design from event-related to block

design. This design would permit a comparison between blocks with only task relevant and passively viewed stimuli as well as between blocks with high and with low distracting task irrelevant and alternatingly presented task relevant stimuli. However, this block design would require finding solutions for the differences in presentation rate and/or spacing for the blocks with and the blocks without interspersed task irrelevant stimuli, thereby potentially over-complicating the original design. Furthermore, it might be advisable to use an FFA localiser with moving instead of static faces, as moving faces have been reported to yield more robust activation (C. J. Fox, Iaria, & Barton, 2009; Schultz & Pilz, 2009). Nonetheless, although the design for the fMRI studies was not optimal, it allowed us to investigate the most notable contrast (task relevant versus high distracting task irrelevant stimuli) both with regard to the task as such and to the impact of *COMT* genotype and aADHD on task-related activation.

Another way the fMRI studies could potentially be improved concerns the relatively long TR of three seconds. Although a long TR was necessary since dorsal as well as ventral structures were of interest here, the field of view in the presented studies also included the cerebellum. While this is of potential importance in the investigation of ADHD, it was not the focus of the research presented here and the recording of its activation unnecessarily prolonged the total recording time. Given the relatively long TRs, it was not possible to include temporal interpolation to partly correct for the different acquisition times of the individual slices during data analysis[15].

Another limitation concerns the aADHD patients included in the third study. Since inclusion and exclusion criteria for this study were very strict, it was not possible to select participants based on their ADHD subtype. This is especially important, as there is some evidence that the inattentive type might represent a disorder that is aetiologically and neurobiologically distinct from the hyperactive/ impulsive and the combined type (Diamond, 2005; Goodyear & Hynd, 1992). As Barkley pointed out several years ago (Barkley, 1997; Barkley, Dupaul, &

[15] Although the usefulness of slice-timing correction is under debate (Friston et al., 2007; Henson, Buechel, Josephs, & Friston, 1999), its use might nevertheless have been advantageous in the analysis of the presented fMRI data.

McMurray, 1990), patients with the inattentive type might be deficient in selective attention and be characterised by a slower cognitive speed. In contrast, patients with the combined type might be easily distracted and more deficient in the area of sustained attention. It would therefore not be unexpected, should these two subtypes show different performance profiles in our selective attention and working memory tasks.

Further analyses addressing this issue, however, would need to take patients' childhood ADHD diagnoses into consideration: Although 19 of the 35 patients who participated in the third study were classified as predominantly inattentive and 15 patients were classified as combined type, we were not able to account for symptom changes over the lifespan. There is some evidence that ADHD symptom profiles change with increasing age (Barkley, 1997; Biederman, Mick, & Faraone, 2000). As hyperactivity declines, patients who would have met diagnostic criteria for the combined type as children, only meet criteria for the predominantly inattentive type in adulthood. These adults' inattention, however, is qualitatively different from that of adults who met criteria for the predominantly inattentive type throughout development (Barkley, 1997). Studies involving aADHD patients would therefore need to retrospectively determine the patients' childhood ADHD subtype and then split the patients now meeting criteria for the predominantly inattentive type into patients who originally met criteria for the combined type and patients who 'truly' have ADHD of the inattentive type. This is – at least at present – highly impracticable. Including 'truly' inattentive, adult age inattentive, and combined type ADHD patients in our investigated sample increased the variance within that sample, thereby reducing the probability to find any significant differences between this sample and healthy controls. While we found correlations for the CAARS Hyperactive/ Impulsive Symptoms as well as the Total ADHD Symptoms scales with performance and/or activation parameters for both the selective attention and the working memory task, no correlations were found for the CAARS Inattentive Symptoms scale, further underscoring the above argument.

With regard to the investigated MPH effects, only limited conclusions can be drawn from our study due to the low achieved power. Future studies should

therefore aim to investigate larger samples in comparable medication trials and consider both response rates and medication effects on neuropsychological as well as neurophysiological functioning, despite the substantial resources this would necessitate. While this is already done with small samples in some studies (e.g. Bush et al., 2008), many investigations still focus on either one or the other aspect, thereby limiting the knowledge that can be attained from these studies. In addition, much information could be gained by splitting the examined patients into responders and non-responders based on an a priori criterion, and by investigating the obtained neuropsychological and fMRI data separately for these two groups. However, the sample size in our study was not sufficient to allow any meaningful analyses of this kind.

Another possible limitation involves the conclusions that can be drawn from the investigations of *COMT* genotype and MPH medication. While the main focus of the literature in these two areas is still on dopamine, both *COMT* genotype and MPH also impact on norepinephrine to a yet unknown extent (Arnsten, 2011; Berridge et al., 2006; Bilder et al., 2004). This is especially important with regard to the selective attention task, as norepinephrine has been hypothesised to improve the signal-to-noise ratio by suppressing task irrelevant and enhancing task relevant stimuli (Pliszka, 2005). While this does not change the main conclusions drawn from our studies, it should be kept in mind that both the reported *COMT* genotype and the MPH effects might be attributable to an unknown degree to the action of norepinephrine instead of dopamine.

In addition, previous findings suggest that *COMT* might have a sexually dimorphic effect (Barnett et al., 2008; Gogos et al., 1998; Harrison & Tunbridge, 2008) and Barnett et al.'s (2008) meta-analysis of performance on the n-back task found that effect sizes increased with the number of female participants in the sample. This limitation should be kept in mind with regard to the *COMT* genotype analyses in the above studies, as cell sizes were small and only here did not allow for a precise balancing of male and female participants. This especially applies to met/met carriers, as the aADHD group was clearly composed of more men than the healthy control group. However, with the exception of the *Digit Span Forward* subtest, the between-group effects in the *COMT* analyses did not incorporate the

met/met group. Consequently, the impact of this gender imbalance might be negligible. Still, as research also points to potential interactive effects of gender and aADHD, with male patients showing more pronounced activation changes than female patients during a working memory task (Valera et al., 2010), a more detailed consideration of this issue might be desirable in future studies.

A final potential criticism pertains to the modified n-back task. Although this task allows for a parametric manipulation of load and thereby maintenance demands (Goldberg et al., 2003), critics point out that it confounds these demands with information updating demands (Bilder et al., 2004). This is problematic, since increased maintenance demands should favour met/met carriers, while increased updating demands should favour val/val carriers. Since the task does not allow for a separate increase of these demands, it could actually be hypothesised to favour val/met carriers, who should be able to fulfil both demands to an intermediate degree. However, while this hypothesis might be supported based on the fMRI activation found in the healthy control participants in the third study, this finding is not in line with the literature (Egan et al., 2001; Mattay et al., 2003; Mier et al., 2010) and more likely due to the small sample size of our study.

6.4 Summary and Outlook

As stated above, this dissertation pursued several goals. The first study investigated selective attention properties of the central executive component during a working memory task. This study replicated and extended previous research by showing that both the task relevance and the degree of distraction of an irrelevant stimulus impacted on early visual processing as measured with EEG. The study furthermore confirmed the influence of stimulus relevance on frontal EEG components and demonstrated a connection of overall activation in frontal areas to suppression efficiency in posterior visual processing areas. Although the impact of (subclinical) symptoms of ADHD on the efficiency of processing modulation could not be confirmed, ADHD symptoms were associated with worse

task performance, indicating some sensitivity of this task for the hyperactive/ impulsive symptoms associated with ADHD.

The goal of the second study was to transfer this task to fMRI, in order to replicate and possibly extend previous findings as well as to assess its sensitivity to changes in neural activation efficiency associated with the *COMT* genotype. These three goals were achieved and we successfully replicated findings of increased frontal and FFA activation during the processing of task irrelevant stimuli compared to task relevant stimuli. In addition, results of differential FFA activation for task irrelevant stimuli depending on how distracting these stimuli were could meaningfully extend previous findings. The task also proved sensitive to the effects of the *COMT* genotype and showed more inefficient activation of val/val compared to met/met carriers in one of the three examined frontal lobe areas.

The third study was the most complex and extensive of this dissertation, and investigated the effects of aADHD, MPH, and *COMT* genotype on working memory in a sample of rigorously selected patients and healthy controls. Since previous studies had shown whole brain between-group differences to be rather small, a particular focus in the analysis of the fMRI data was placed on activity in the task-positive/ attention network. A clinical effect of MPH was visible in this study, but the symptom improvement of aADHD patients taking MPH compared to placebo was non-significant on the investigated scales or with regard to response rates. These non-significant findings have to be attributed to insufficient power of this study. As noted above and in spite of the low power, however, a beneficial effect of MPH was clearly visible.

This study is one of the first investigations, which explored the neuropsychological effects *COMT* in a sample of aADHD patients and a comparable healthy control group, and showed an interactive effect of these two factors. While there was no main effect of *COMT* on the investigated neuropsychological tests, aADHD patients did not seem to be able to profit from task characteristics benefitting a particular genotype in the same way healthy controls did.

The fMRI data in this study showed that the selective attention task successfully activated the task-positive network when high distracting task

irrelevant and task relevant stimuli were compared. In addition, ROI analyses yielded decreased activation in the right DLPFC of the patient group. Contrary to the second (fMRI) study, this third study also showed an association of activation in this cluster and FFA suppression efficiency, and suppression efficiency was significantly worse in patients with higher hyperactive/ impulsive symptoms. No significant effect of MPH could be found in this study.

In contrast, the n-back task, which concentrated more exclusively on working memory without a specific focus on selective attention, showed more activation in nodes of the task-positive network in the group with aADHD in the absence of behavioural performance differences. Furthermore, more hyperactive/ impulsive symptoms were associated with stronger network activation and more activation was also correlated with better performance. This pattern of results supports the conclusion of compensatory activation in the aADHD group. In addition, activation in the SFG was increased in patients taking MPH compared to placebo, which is in line with previous reports of MPH up-regulating frontal nodes of the task-positive network. Furthermore, we could replicate the *COMT* effect of more inefficient frontal activation in val/val carriers across all participants. In addition, we found an interaction effect of *COMT* genotype and aADHD. Based on this finding, we propose a left shift of aADHD patients on the hypothesised inverted U-shaped cortical response function to dopamine, as aADHD seemed to exacerbate the hypothesised negative impact of two val-alleles on cortical efficiency.

It should be noted that the number of fMRI data analyses, which could be reported in this dissertation was naturally limited and that consequently only the broadest and most comprehensive analyses could be described here. It might therefore prove beneficial to exploratorily analyse further aspects of the data using more liberal methods and statistical thresholds.

Still, future studies that include larger sample sizes are clearly needed. Such studies could build on our findings by investigating the complexity of the interactive impact of *COMT* genotype and aADHD on neuropsychological test results. These studies should also consider the impact on cortical activation measured with fMRI, but also on medication response and adverse effects. It might

also be advisable to investigate *COMT* haplotypes (Nackley et al., 2006) instead of single SNPs, as this might provide further differentiation of the obtained results. In addition, research on ADHD might benefit from adopting a stronger network perspective. Whole brain between-group comparisons almost always yield small – if any – differences. In contrast, the network perspective seems much more promising. While several studies already investigated activation and connectivity of the default mode network at rest (e.g. Fair et al., 2010), more research using multivariate analysis methods could still be done on the activation of task-positive networks and the deactivation of task-negative networks during task completion (Liddle et al., 2011). In addition, the interaction of cortical and subcortical network structures as well as possible abnormal connectivity in ADHD require more in-depth investigations (Castellanos & Proal, 2012; De La Fuente, Xia, Branch, & Li, 2013; Sun et al., 2012; Wolf et al., 2009). The inspired meta-analysis by Cortese et al. (2012), which connected the results from previous fMRI studies to hypothesised network activation in ADHD and healthy controls is certainly a step in the right direction and provides many interesting suggestions for future research.

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8 Appendix

8.1 Study 1: EEG Parameters of Selective Attention

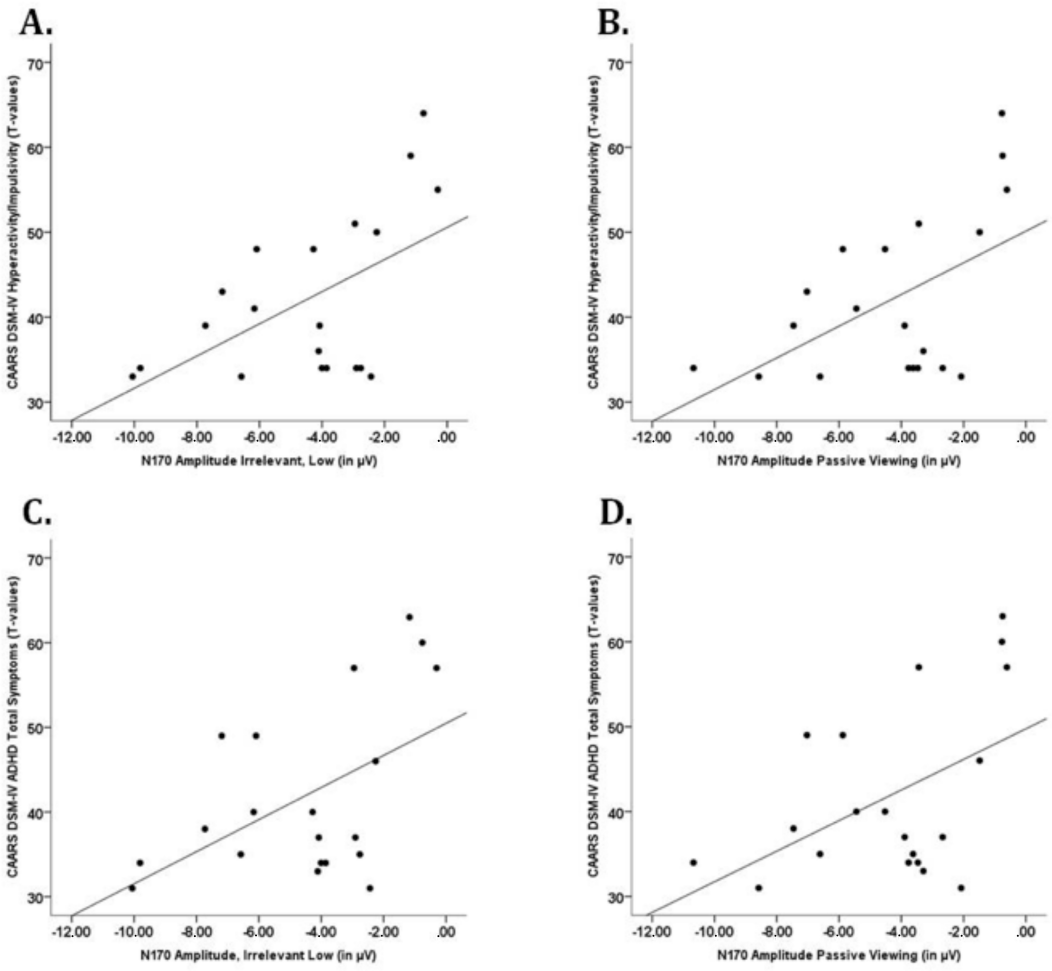

Figure 8.1: Scatter plots and linear regression lines for N170 amplitudes and CAARS DSM-IV Hyperactive/ Impulsive and Total Symptoms subscales. Each dot represents one participant.

8.2 Study 2: fMRI Parameters of Selective Attention

Table 8.1: MNI coordinates of significant between-group peak voxel difference for the selective attention task.

Anatomical region	MNI coordinates
Selective attention task: val/val versus met/met carriers	
- Right medial frontal gyrus	12 2 64

8.3 Study 3: Double-Blind Placebo-Controlled Trial

Table 8.2: Inclusion and exclusion criteria for ADHD patients

Inclusion criteria

Participants must fulfil all of the following criteria:

1. Only participants will be included who (1) fulfil the diagnostic criteria defined in the guidelines for the diagnosis of ADHD in childhood and adulthood, and who (2) would be treated with MPH also for clinical indications outside the study.
2. Provision of written informed consent.
3. A diagnosis of aADHD by Diagnostic and Statistical Manual of Mental Disorders – Fourth Edition (DSM-IV).
4. Females and males aged 18 to 50 years.
5. Female patients of childbearing potential must be using a reliable method of contraception and have a negative urine human chorionic gonadotropin (HCG) test at enrolment.
6. Able to understand and comply with the requirements of the study.
7. Right-handed according to Edinburgh Handedness Inventory (Oldfield, 1971).
8. German as first language.
9. Caucasian ethnicity.

Exclusion criteria

Any of the following is regarded as a criterion for exclusion from the study:

1. Pregnancy or lactation; women capable of childbearing are required to use a reliable method (Pearl-index < 1%) of contraception (e.g. hormonal treatment, intrauterine device, vasoligation in the partner, sexual abstinent).
2. Any current DSM-IV Axis I disorder not defined in the inclusion criteria requiring current additional treatment.
3. Motor tics, siblings with tics, or positive family history or diagnosis of Tourette syndrome.

4. Patients who, in the opinion of the investigator, pose an imminent risk of suicide or a danger to self or others.
5. Known intolerance or lack of response to MPH, as judged by the investigator.
6. Present pre-treatment with MPH (within the last three months prior to study treatment).
7. Intake of MAO-inhibitors within the last 14 days prior to study treatment.
8. Medical conditions that would affect absorption, distribution, metabolism, or excretion of study treatment.
9. Unstable or inadequately treated medical illness (e.g. Congestive Heart Failure/ CHF, angina pectoris, hypertension, narrow angle glaucoma, hyperthyroidism, thyrotoxicosis, cardiac arrhythmia, cardiac infarction) as judged by the investigator.
10. Epilepsy.
11. An absolute neutrophil count (ANC) of ≤ 1.5 x 10^9 per litre.
12. Involvement in the planning and conduct of the study.
13. Previous enrolment or randomisation of treatment in the present study.
14. Participation in another drug trial within 4 weeks prior to enrolment into this study.
15. Moderate, severe, or profound mental retardation.
16. Heart pacemakers, cochlea implants, other metal parts in the head outside the mouth.

The dispensed MPH and placebo medication consisted of lactose monohydrate, magnesiumstearat, cellulose powder, and microcristalline cellulose and was provided by MEDICE Pharma GMBH & Co. KG, Iserlohn, Germany. It was labeled as follows:

Methylphenidat-HCl 10 mg Tabletten oder Placebo-Tabletten
180 Tabletten zum Einnehmen
Woche 1-6
Patienten-Nr.:
Studien-Nr.: W004PS0108_1
Ch.-B.:
Verwendbar bis:
Zur klinischen Prüfung bestimmt
Dosierung gemäß der Anweisung des Prüfarztes
Außerhalb der Reichweite von Kindern lagern
Nicht über 25°C lagern
Nicht verbrauchte Tabletten an den Arzt zurückgeben!
Klinik und Poliklinik für Psychiatrie, Psychosomatik und Psychotherapie, Würzburg, Telefon: 0931 – 201 77000

Table 8.3: MNI coordinates of significant or trend level between-group differences for the different tasks.

Anatomical region	MNI coordinates
Selective attention task: healthy controls versus patients with ADHD	
- Right DLPFC	42 44 31
N-back task: healthy controls versus patients with ADHD	
- Left anterior IPS	-36 -49 40
- Right inferior/middle frontal gyrus	45 11 37
- Left DLPFC	-39 35 25
- Right posterior IPS	15 -76 46
- Right anterior IPS	39 -49 49
N-back task: ADHD patients with MPH versus placebo	
- Right superior frontal gyrus	24 50 37

8.3.1 Selective Attention Task

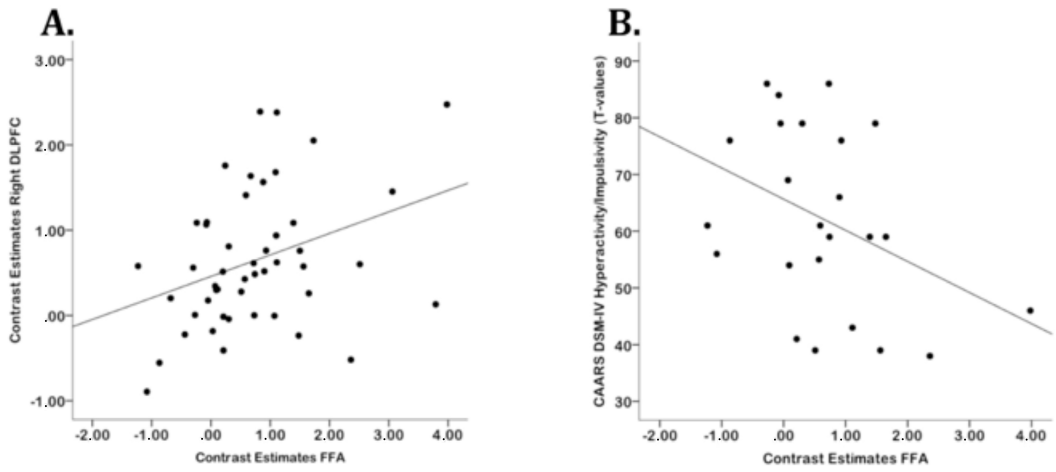

Figure 8.2: Scatter plots and linear regression lines for contrast estimates (high distracting task irrelevant minus task relevant condition) in the right DLPFC and the FFA as well as CAARS DSM-IV T-scores and FFA contrast estimates for the patient group. Each dot represents one participant.

8.3.2 N-Back Task

Table 8.4: Correlation coefficients (r) and p-values of peak voxel contrast estimates with correct as well as incorrect performance for the entire sample, as well as correlation coefficients (r) and p-values of contrast estimates in these clusters with T-scores for the CAARS DSM-IV Hyperactive/ Impulsive Symptoms and CAARS DSM-IV Total ADHD Symptoms scales for the patient sample.

Anatomical region	Performance (correct) *r* (*p*-value)[1]	Performance (incorrect) *r* (*p*-value)[1]	*CAARS* hyper./impuls. *r* (*p*-value)[2]	*CAARS* total symptoms *r* (*p*-value)[2]
Left anterior IPS	.13 (n.s.)	.19 (n.s.)	.46 (.01)	.51 (.01)
Right IFG/MFG	.22 (n.s.)	.34 (.01)	.38 (.04)	.41 (.03)
Right posterior IPS	.32 (.02)	.47 (<.001)	.42 (.02)	.32 (.09)
Right anterior IPS	.20 (n.s.)	.36 (.01)	.20 (n.s.)	.27 (n.s.)

Note. [1] degrees of freedom (df) = 56; [2] df = 27.

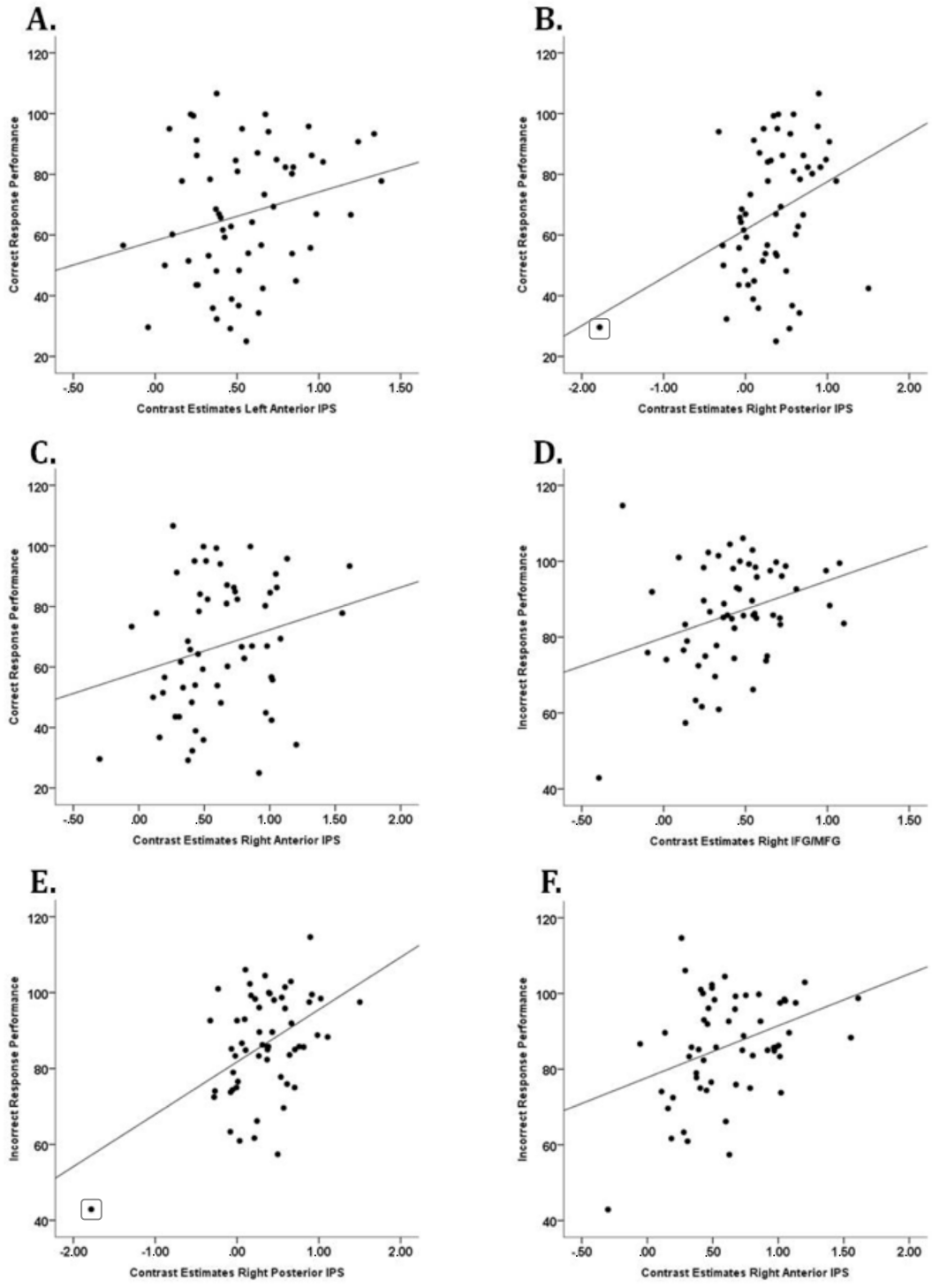

Figure 8.3: Scatter plots and linear regression lines for contrast estimates (2-back minus 0-back condition) and task performance. Each dot represents one participant. Correlations for the right posterior IPS (B. and E.) retained significance after the extreme outlier (in grey box) was excluded.

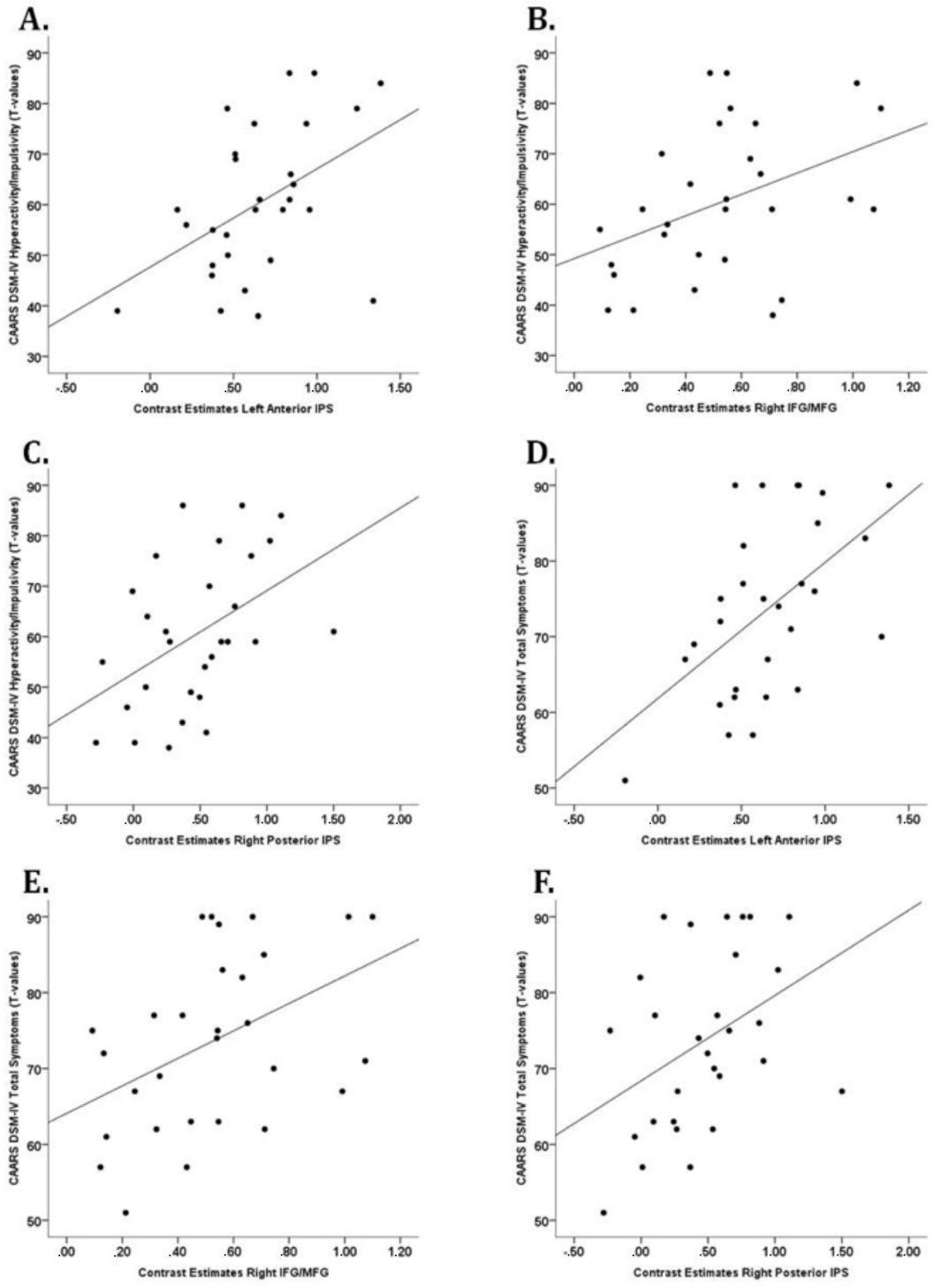

Figure 8.4: Scatter plots and linear regression lines for contrast estimates (2-back minus 0-back condition) and CAARS DSM-IV T-values for the patient group. Each dot represents one participant.

8.3.3 Interaction of *COMT* Genotype and ADHD

Peak voxel contrast estimates

1. Left anterior IPS:

   - Significant interaction of *COMT* genotype and ADHD ($F_{(2,50)} = 4.21$, $p = .02$).
     - Significantly higher activation of ADHD val/met carriers ($p < .001$) and ADHD val/val carriers ($p = .03$) compared to healthy controls.

2. Right IFG/MFG:

   - Significant interaction of *COMT* genotype and ADHD ($F_{(2,50)} = 4.64$, $p = .02$).
     - Significantly higher activation of ADHD val/met carriers ($p = .003$) and ADHD val/val carriers ($p = .04$) compared to healthy controls.

8.4 Affidavit/ Eidesstattliche Erklärung

Affidavit

I hereby confirm that my thesis entitled "The Impact of Adult Attention Deficit/ Hyperactivity Disorder, Methylphenidate, and the *COMT* Val^{158}Met Polymorphism on Selective Attention and Working Memory" is the result of my own work. I did not receive any help or support from commercial consultants. All sources and/ or materials applied are listed and specified in the thesis.

Furthermore, I confirm that this thesis has not yet been submitted as part of another examination process neither in identical nor in similar form.

Würzburg,

Place, Date Signature

Eidestattliche Erklärung

Hiermit erkläre ich an Eides statt, die Dissertation „Der Einfluss von Aufmerksamkeitsdefizit/ Hyperaktivitätsstörung bei Erwachsenen, Methylphenidat, und des *COMT* Val^{158}Met Polymorphismus auf selektive Aufmerksamkeit und Arbeitsgedächtnis" eigenständig, d.h. insbesondere selbständig und ohne Hilfe eines kommerziellen Promotionsberaters, angefertigt und keine anderen als die von mir angegebenen Quellen und Hilfsmittel verwendet zu haben.

Ich erkläre außerdem, dass die Dissertation weder in gleicher noch in ähnlicher Form bereits in einem anderen Prüfungsverfahren vorgelegen hat.

Würzburg, den

Ort, Datum Unterschrift

8.5 Curriculum Vitae

8.6 Publications

Müller, L. D., Guhn, A., Zeller, J. B., **Biehl, S. C.**, Dresler, T., Hahn, T., Fallgatter, A. J., Polak, T., Deckert, J., Herrmann, M. J. (in press). Neural correlates of a standardized version of the Trail Making Test in young and elderly adults: a functional Near-Infrared Spectroscopy study. *Neuropsychologia*.

Biehl, S. C., Ehlis, A. C., Müller, L. D., Niklaus, A., Pauli, P., & Herrmann, M. J. (2013). The impact of task relevance and degree of distraction on stimulus processing. *BMC Neuroscience, 14*(107).

Gschwendtner, K. M., **Biehl, S. C.**, Mühlberger, A., Sommer, C., Kübler, A., Reif, A., & Herrmann, M. J. (2012). The relationship between valence, task difficulty, and the COMT v*al*^{158}*met* polymorphism in disengagement processes. *Journal of Psychophysiology, 26*(3), 124-131.

Biehl, S. C., Dresler, T., Reif, A., Scheuerpflug, P., Deckert, J., & Herrmann, M. J. (2011). Dopamine Transporter (DAT1) and Dopamine Receptor D4 (DRD4) genotypes differentially impact on electrophysiological correlates of error processing. *PLoS ONE, 6*(12).

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Herrmann, M. J., **Biehl, S. C.**, Jacob, C., & Deckert, J. (2010). Neurobiological and psychophysiological correlates of emotional dysregulation in ADHD patients. *ADHD Attention Deficit and Hyperactivity Disorders, 2*(4), 233-239.

Herrmann, M. J., Schreppel, T., **Biehl, S. C.**, Jacob, C., Heine, M., Boreatti-Hummer, A., et al. (2009). Emotional deficits in adult ADHD patients: an ERP study. *Social Cognitive and Affective Neuroscience, 4*(4), 340-345.

8.7 Danksagung